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Year in review in intensive care medicine, 2005. II. Infection and sepsis, ventilator-associated pneumonia, ethics, haematology and haemostasis, ICU organisation and scoring, brain injury

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This review intends to summarize all articles published in Intensive Care Medicine in 2005, grouped by specific topics.

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Infection and sepsis

Prediction and outcome of infections

Because of their poor prognosis, patients with advanced haematological malignancies may be denied ICU admission. In a prospective cohort study of 172 patients with haematological malignancy admitted to a single ICU over a 4-year period, Benoit et al. [1] examined hospital and 6-month mortality after stratification on whether an infection was present, suspected or absent on ICU admission. After adjustment for the severity of critical and underlying haematological illness and the duration of hospitalisation before admission, documented ([odds ratio] OR 0.20; $p = 0.006$) and clinically suspected bacterial infection (OR 0.18; $p = 0.002$) were found associated with a more favourable outcome than nonbacterial complications leading to admission. The authors conclude that since the former have a better outcome, such patients should receive full supportive care for an adequate period of time.

Brivet et al. [2] analysed retrospectively 140 patients admitted over a 10-year period with acute meningitis to determine clinical variables associated with a bacterial rather than a viral aetiology. They found that the presence of one or more sign of severity (altered consciousness, seizures, focal neurologic findings or shock) and a CSF neutrophil count above 1,000/mm^3 were associated with a bacterial aetiology, whereas, CSF glucose and protein levels were not. The editorial by W. Zimmerli [3] emphasises that although this approach allows to recognise accurately those patients who rapidly need antibiotics and supportive care in an intensive care unit, withholding antibiotics in all patients without such signs of severity would be premature, at least until the results of this study are confirmed in a prospective evaluation of patients with early presentation of bacterial meningitis, who would most benefit from early antibiotic therapy.

Bacteraemia and sepsis

Laupland et al. [4] analysed a large cohort ($n = 4,845$) of patients admitted during a 33-month period to a regional critical care system in Canada to examine the long-term (1-year) outcome of ICU patients admitted with bacteraemia (BSI). Five percent ($n = 251$) had bacteremic sepsis or shock. The 3-month and 1-year mortality were 30% and 36% for bacteraemic sepsis and 57% and 61% for bacteraemic shock. Analysing the population who died between 28 days and 1 year post-ICU discharge ($n = 1,054$), the authors found that BSI-associated sepsis was associated with a 2.15-fold increased risk of death (vs early death), after adjustment for severity of illness, age, nursing workload, and other diagnostic categories. This study thus confirms earlier findings by Quartin et al. and others [5], and provides one more piece of evidence that sepsis impacts mortality well beyond the conventional 28-day end point. In an accompanying editorial, P. Dodek [6] also recommend examining longer-term effects of current interventions aimed at improving the outcome of septic patients.

A high incidence of subsequent infection, notably primary bacteraemia, has been reported in patients resuscitated from cardiac arrest. Tsai et al. [7] re-examined this question in a prospective cohort of 117 patients with out-of-hospital cardiac arrest who survived > 24 h. Pneumonia and bacteraemia occurred, respectively, in 43% and 9% of patients, and the overall incidence of infection was 71% within the first 7 days. Most infections were caused by Gram-negative bacilli, but *Staphylococcus aureus* was the predominant organism. These early infections did not appear to influence outcome of patients, perhaps because of adequate treatment and of the major influence of neurological outcome.

Catheter-associated infections

Taking blood for culture from the catheter and a peripheral vein is recommended for diagnosing catheter-related infection (CRI). Tanguy et al. [8] examined the yield of central blood cultures in 135 episodes of sepsis of unknown origin in patients with an indwelling catheter. Central blood cultures were positive in 18 episodes, including all three episodes of catheter-related bacteraemia (CRB) and seven episodes of secondary bacteraemia. All CRB gave positive central blood culture in < 24 h. There were two false-negative (non-bacteraemic CRI) and six false-positive central blood cultures. The authors conclude that central blood cultures have a reasonably negative predictive value to rule out CRI.

It remains unclear whether haemodialysis catheters (HDC) should be replaced routinely at scheduled intervals. Harb et al. [9] re-examined this question in a series of 79 HDC left in place for various lengths of time in critically ill cancer patients. They found that the incidence of colonisation and infection was low (5.4 and 1.8 per 1,000 days), did not increase with indwelling time, and did not differ from that of other short-term central venous catheters. These results do not support the routine scheduled replacement of HDC, similarly to other short-term central venous catheters.

Candida colonisation and infection

Charles et al. [10] examined the yield of weekly surveillance cultures at multiple sites to determine the "colonisation index" in medical ICU patients. They found that a 50% index was reached in nearly 40% of patients, although almost exclusively in those with *Candida* colonisation on admission. They also confirmed that administration of broad-spectrum antibiotics was the major risk factor

for multiple-site colonisation, which the authors suggest is a factor amenable to intervention.

Prophylaxis has not been clearly shown to be effective in ICU patients, except in selected high-risk patient groups. In attempt to address this problem of widespread *Candida* colonisation in ICU patients, Normand et al. [11] performed an open randomised trial of oral nystatin prophylaxis (3 million units/day) vs no prevention in 98 mechanically ventilated patients to prevent *Candida* colonisation. Using a blinded assessment of colonisation, they found a 25% acquisition rate of *Candida* colonisation in controls vs none in treated patients. However, no patient in either group developed systemic *Candida* infection, probably because the study was conducted in a low-risk group, as noted in the accompanying editorial by Eggimann et al. [12].

To examine potential differences in practices of infectious-disease specialists and ICU physicians regarding management of *Candida* infections, Eggimann et al. [13] administered a structured questionnaire to 116 Swiss physicians of both groups using clinical vignettes. Overall, infectious-disease specialists were more conservative in most instances and less often treated patients with, e.g., catheter-related bacteraemia or primary peritonitis. Conversely, ICU physicians reported using fewer new drugs than infectious-disease physicians.

Control of MRSA

Lucet et al. [14] report the successful long-term (7-year) effect of a multifaceted approach to control methicillin-resistant *Staphylococcus aureus* (MRSA) in three ICU of the same hospital, including screening of carriers and isolation precautions, followed by the introduction of waterless alcohol-based hand rubbing for hand hygiene. Despite a continuously high prevalence of MRSA carriage on admission (6%) and reintroduction of MRSA in these ICUs, a substantial reduction in the MRSA acquisition rate was recorded after introduction of hand rubbing, from 7% to 2.8%. These results confirm in a different setting and a longer term period, those obtained by Pittet et al. in Geneva [15], and that control of MRSA spread can be achieved in ICUs despite high colonisation pressure.

Ventilator-associated pneumonia (VAP)

After more than 20 years of debate and hundreds of papers on the optimal strategy for diagnosing and treating VAP in mechanically ventilated critically ill patients, the major question in 2005 for ICU physicians was to improve the use and avoid the misuse of antibiotics: (1) an appropriate diagnostic strategy minimises the risk of indiscriminate administration of antimicrobial agents in all patients with clinical signs and symptoms suggestive of VAP; (2) inadequate and/or delayed initial antibiotic therapy is associated with fatality. Difficulties in treating such patients are maximal in cases of VAP due to highly resistant organisms: MRSA, extended spectrum beta lactamase producing (ESBL) enterobacteriaceae, non-fermenting gram-negative bacilli. These pathogens were identified as responsible for pneumonia in patients previously treated with antibiotics and/or in case of late-onset VAP, i.e., VAP occurring more than 5–7 days after initiation of mechanical ventilation [16]. It is, however, important to realize that each ICU has its own bacteriology, and that variations in the resistance profiles are frequent, from one hospital to another or from one unit to another in the same hospital, and that patterns of resistance vary over time.

A majority of papers published in 2005 concerning VAP were investigating pneumonia due to multiresistant bacteria and/or late-onset pneumonia with the underlying objective of improving antimicrobial treatment, particularly the choice of initial antimicrobial therapy.

Leone et al. tried to find risk factors for the development of late-onset VAP in 159 severe trauma patients receiving selective digestive decontamination (SDD) consisting of polymixin E, gentamicin and amphotericin B [17]. Late-onset VAP was diagnosed in 90 (56%) patients. Interestingly, only 2% of pneumonia cases were due to MRSA; 7% of gram-negative bacteria were multiresistant to antibiotics and *Pseudomonas aeruginosa* was isolated in only two patients. Risk factors for acquiring late-onset VAP in this population were: the use of non-depolarizing muscle relaxant agents for intubation, duration of intubation and of ICU stay, and prior tracheal colonisation. Prior antimicrobial therapy seems to confer protection. Except the identification of a possible impact of SDD on epidemiology of VAP in trauma patients, particularly an unusually low incidence of multiresistant bacteria as responsible for late-onset VAP, this study did not really explain the complex relationship between severity of underlying medical condition, prior antibiotic usage, occurrence of VAP and responsible pathogens in patients receiving SDD.

Garnacho–Montero et al. studied predictors and prognostic factors of VAP due to imipenem-resistant *Acinetobacter baumannii* [18]. During the 54-month study period, several outbreaks of *A. baumannii* were observed, which constitute a possible risk of misinterpretation in such an analysis of risk factors, and a possible explanation for the specially high rate of *A. baumannii* VAP (51% of all isolated pathogens, including imipenem-resistant *A. baumannii* in 33%). Not surprisingly, prior antibiotic use was found to be associated with VAP due to this pathogen, and prior imipenem exposure was associated with imipenem-resistant *A. baumannii* VAP. The prognosis of patients developing *A. baumannii* lung infections was influenced by variables similar to that identified as having a prognostic value in the case of VAP due to other pathogens: severity of illness at the time of

onset of VAP was selected by the multiple regression analysis as the only independent predictor of mortality. In contrast, adequate initial antimicrobial therapy was identified as a protective factor.

Among pathogens responsible for late-onset VAP, *Pseudomonas aeruginosa* and *Acinetobacter* species have been found to be resistant to many currently available (and usually prescribed) antimicrobial agents. Because only a few antibiotics remain effective in this context, antibiotics which had been abandoned for serious adverse effects merit reevaluation. Reina et al. have performed a study to evaluate the renal toxicity and the efficacy of intravenous colistin compared to conventional antibiotics in 185 severe ICU-acquired infections due to *P. aeruginosa* and *Acinetobacter* species, including VAP in 62% of cases [19]. No colistin-resistant microorganisms were isolated in this study. The authors concluded that colistin was as safe (no difference in renal function) and as effective (no differences in clinical cure and mortality rates) as other antimicrobial agents (mainly carbapenems in this study) for the treatment of infections due to non-fermenting gram-negative bacilli. This study confirms the results of one report that documented the efficacy and safety of intravenous colistin in patients with carbapenems-resistant *Acinetobacter* VAP [20].

Colonisation of the upper airways and tracheobronchial tree is a well-known risk factor for the development of VAP. Modulation of oropharyngeal colonisation by combination of oral antibiotics associated or not with systemic therapy, has been identified as a way to reduce the frequency of VAP. However, the specific role of systemic antibiotics in the prevention of VAP is unclear: some studies identify antibiotic administration as a risk factor for the development of late-onset VAP, whereas, other studies show that prior antibiotic exposure confers protection for VAP, particularly early-onset VAP. A prospective randomised open study was conducted by Acquarolo et al. to evaluate the impact of a 3-day ampicillin-sulbactam prophylaxis on the occurrence of early-onset (< 4 days of mechanical ventilation) VAP in comatose patients compared to a group of patients without antibiotic prophylaxis [21]. The study was interrupted after an interim analysis at 1 year, when 42 patients had been enrolled (the initially calculated sample size was 142 patients). Thirty-eight patients were evaluable, 19 in each group. The incidence of early-onset VAP was 21.0% in the ampicillin-sulbactam group and 57.9% in the control group ($p = 0.022$). In contrast, the two groups were comparable in terms of late-onset VAP incidence (52.6% and 50.0%; $p = 0.75$), as well as outcome parameters such as duration of Mechanical Ventilation (MV), duration of ICU stay and ICU mortality. Unfortunately, the small number of patients enrolled, extracted from a limited population of comatose patients, and the small number of microbiological isolates, precluded a definitive answer to the question of the prevention of VAP with antibiotics in a unselected population of ICU patients treated with mechanical ventilation.

Recently, the classic relationships between early-onset pneumonia and sensitive pathogens vs late-onset pneumonia and multiresistant pathogens have been questioned: Ibrahim et al. reported that pathogens associated with early-onset and late-onset VAP may be similar and frequently multiresistant [22]. Giantsou et al. re-examined these data by comparing the causative pathogens of 191 patients with early-onset (< 7 days) and 217 with late-onset (≥ 7 days) VAP diagnosed by bronchoscopic BAL [23]. No difference was noted in the distribution of multiresistant pathogens (79% vs 85%), *P. aeruginosa* (42% vs 47%), or MRSA (33% vs 30%) between early-onset and late-onset VAP. Interestingly, 99% of patients with early-onset VAP caused by *P. aeruginosa* and/or MRSA were receiving antimicrobial therapy prior to the development of pneumonia. Hospital mortality observed in this study was higher in early-onset VAP caused by *P. aeruginosa* and/or MRSA than in VAP due to other pathogens. In their related editorial, Chastre et al. emphasize the need to tailor initial antibiotic therapy to local patterns of antimicrobial susceptibilities by having a current and updated knowledge of local bacteriologic patterns [24]. This point is probably more important than guiding the choice of initial treatment only on the time-onset of infection. The results of the study by Giantsou et al. may have very important therapeutic implications: based on its results, early-onset VAP should be treated with a combination of agents that can provide a very broad spectrum of coverage. However, the need to ensure that patients receive an appropriate antibiotic regimen should not lead to indiscriminate use of antibiotics in the ICU.

It is worth noting that in all studies published in 2005 in Intensive Care Medicine investigating diagnosis, epidemiology, risk factors, treatment and/or prevention of VAP, the authors insisted on the use of quantitative cultures of bronchoscopic techniques to "give more accurate results than endotracheal aspirates" [23]. These techniques, when they are performed before introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, initially with the results of direct examination of appropriate sample (preferentially liquid obtained with BAL) and after 48 h, at the time of the results of quantitative cultures to adapt, interrupt, or de-escalating antibiotic treatment, in a manner that is safe and well-tolerated by patients. On the other hand, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinically suspicious infection.

Besides these important concerns on the optimal use of antibiotics for the treatment of one of the most devastating infections acquired in the ICU, with potentially immediate consequences on the management of

patients treated with mechanical ventilation, intensivists tried to evaluate the diagnostic value of new techniques, procedures or dosages. Determann et al. conducted a study to determine the diagnostic role of soluble triggering receptor expressed on myeloid cells (sTREM-1) [25]. To do that, they collected blood and bronchial lavage fluid obtained with non-directed BAL on alternate days in nine patients with VAP and 19 without VAP [25]. Plasma levels did not change in time in both groups. In contrast, concentrations of sTREM-1 in bronchial lavage fluid did not change in the control group, but increased significantly before the diagnosis of VAP in the other group. The reported sensitivity and specificity of one dosage > 200 pg/ml on the day of VAP, or of an increase of at least 100 pg/ml before the onset of VAP do not allow determining the exact place of this diagnostic technique in clinical practice today, but suggest that sTREM-1 is a biological marker potentially useful for pneumonia.

Ethics

Four articles published in the Journal have highlighted the growing interest for cultural and geographical variability observed during the end-of-life (EOL) decision-making process for critically ill dying patients. Research on this important issue had been encouraged during the Fifth International Consensus Conference in Critical Care [26], and the Journal published in 2005 experience from Lebanon, New Zealand, the United kingdom and from a collaborative group from Europe. An important common point to these studies is that they all indicate the need to apply recent recommendations and eventually implement international recommendations. Yazigi and colleagues have described how end-of-life decisions were implemented for 45 patients in one Lebanese ICU [27]. Decisions to forgo life-sustaining therapies were implemented in about half the patients who died. Therapies were withheld in 38% and withdrawn in 7% of patients who died. Interestingly, nurses were part of the decision in 74% of the cases. Family members shared in the decision in 79% of the cases; and decisions were noted in the patient's medical record in 77% of the cases. As pointed out in the accompanying editorial from Pochard and Abroug [28], little is known about the frequency and characteristics of end-of-life practices in oriental countries where cultural values and religious influences differ from those in North America and Europe. The results from this study provide insights into the evidence that only minor differences can be observed between practices in this Lebanese ICU and in our Occidental ICUs. Ho and colleagues investigated how intensive care nurses were involved in end-of-life decisions in New Zealand [29]. They performed a survey of 611 ICU nurses from 35 ICUs. Seventy-eight percent of the answering nurses reported that they were actively involved in EOL decisions. Senior nurses in general, and European nurses were more frequently involved than Asian or Pacific Islander nurses. Most (68%) of the respondents reported that an increased involvement of the nurses in the EOL decision-making process was timely and would increase nurse's satisfaction. Wunsch and colleagues described the epidemiology of active treatment withdrawal in a nationally representative cohort of English ICUs [30]. Among the 118,199 adult admissions to 127 ICUs in England, Wales and Northern Ireland, between 1995 and 2001, a decision to forgo life-sustaining therapies was implemented in 9.9% of the patients. About 32% of the hospital deaths occurred after the decision to withdraw active treatment. Strikingly, the percentage of ICU deaths that occurred after the decision to withdraw active treatment ranged between 1.7% and 96.1%, and this variability remained after accounting for case-mix differences in admissions. Cohen and colleagues reported data from the ETHICUS study, detailing how EOL practices were implemented in 37 European ICUs in 17 countries and how much intensivists all over Europe need to improve their communication skills [31]. ICU physicians collected data on 4,248 patients, including only 5% of competent patients. Overall, family members were informed of the EOL decision in 88% of the cases and were involved in the decision-making process in only 38% of the cases. Regarding communication with patients and families during the decision-making process, physicians in the northern countries more frequently had information about patient's wishes (31%) and discussion with families (88%) than in central (16%, 70%) or southern (13%, 48%) countries.

Sluiter and colleagues sought to enhance communication in their pediatric ICU (PICU) by implementing multidisciplinary structured work-shift evaluations [32]. They measured, in all 61 PICU staff members, (1) quality and process of the implementation through pre-structured checklists during the 3 months of implementation, (2) a subjective evaluation of feedback training on team communication as anticipated action and on the level of communication, and (3) emotional exhaustion complaints and work-related fatigue, before and after the intervention. The intervention increased staff satisfaction with communication between caregivers and decreased emotional exhaustion.

Young and colleagues measured symptoms of anxiety and depression in patients and relatives after discharge from intensive care [33]. Using the Hospital Anxiety and Depression Scale, they gathered data from 20 patients, family members, and 15 elective cardiac surgery patients and their relatives. Family members of critically ill patients presented more frequently with symptoms of anxiety than patients themselves, and more frequently with symptoms of depression than family members from cardiac surgery patients.

Haematology and haemostasis

Crowther and colleagues sought to identify laboratory tests that reliably predict deep venous thromboembolism (DVT) [34]. In a prospective cohort study they measured a panel of hypercoagulability markers (protein C, protein S, activated protein-C resistance ratio and antithrombin) at ICU admission in 197 consecutive patients. In addition, six commercial D-dimer assays were performed serially during the ICU stay in medical-surgical ICU patients who were screened for DVT with biweekly lower-limb compression ultrasonography. The biological marker was not relevant to predict the occurrence of DVT. The low performance (poor specificity and poor positive predictive value) of D-dimers has been highlighted in an editorial by Le Gal and Bounameaux [35]. Indeed, D-dimer testing is widely used as a first-line test, at least in outpatients with suspected DVT, as DVT can be ruled out in about 30% of such patients without further invasive and/or expensive testing. In the study from Crowther, among the medical-surgical critically ill patients, only 3.6% had negative bedside D-dimer tests, which definitely precludes the use of these tests in ICU patients.

Sivula and colleagues performed a retrospective study in 494 consecutive patients to assess the value of a disseminated intravascular coagulation (DIC) score in predicting day-28 mortality in intensive care patients [36]. Mortality was higher in the 95 (19%) patients with overt DIC than in other patients (40% vs 16%). However, overt DIC was not an independent predictor of day-28 mortality. Plasma antithrombin, but not plasma fibrinogen, had a good discriminative power for the diagnosis of overt DIC. Platelet count, plasma D-dimer, and Owren-type prothrombin time activity discriminated well the patients with and without overt DIC.

Pene and co-authors performed a multicentre retrospective study of prognosis in critically ill patients with severe adult thrombotic microangiopathies (i.e., thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS) [37]. They collected clinical and biological data in 63 patients (19 TPP, 18 HUS and 26 undetermined) admitted into 14 French ICUs from January 1998 to June 2001. Mortality rate was 35% and was intimately linked to the extent of neurologic failure. Strikingly, the use of plasma exchange was independently associated with survival. Although the results are not adjusted for the volume of plasma provided in the two treatment groups, this study provides arguments for the use of plasma exchange as the first-line therapy in critically ill patients with thrombotic microangiopathies.

ICU organisation, scoring

Severity of illness

Risk adjustment in intensive care medicine has become the gold standard to draw inferences from mortality rates. This includes clinical trials and observational studies, as well as performance evaluation of ICUs. Current systems, however, have been shown to lack prognostic performance. Aegerter et al. [38] have thus tried to update one of the most widely used risk-adjusted systems, the Simplified Acute Physiology Score (SAPS) II. They analysed data from 32 ICUs of the Parisian area and used logistic regression techniques to customize the SAPS II, i.e., to adapt this system to their case mix. Although their newly developed model showed improved overall performance, it did not perform well in different subgroups of patients, and a big part of the variation of outcomes between different centres remained thus unexplained. For this reason, the authors conclude that current risk-adjustment systems cannot be used as a definite evaluation tool. The fact that even customisation is not able to solve all the model-inherent problems of current risk-adjustment systems was also one of the starting points for the SAPS 3 project. This successor of the previously mentioned SAPS II was developed and now published by Metnitz [39] and Moreno [40] on behalf of the SAPS 3 Outcomes Research group. In part 1 of the report, the objective of the study, conduct of the project and the resulting cohort were described. The objective of the SAPS 3 project was to cope with the above-stated problems by developing a new model for improved risk adjustment in critically ill patients. Another important goal was to make the new model available free of charge, for use in the scientific community. Part 2 of the report described the development of the SAPS 3 admission score. For this score, data recorded within ± 1 h of ICU admission were used, describing prior chronic conditions and diseases, related circumstances and physiologic derangement at ICU admission. Twenty variables made up the final model, which exhibited good discrimination and calibration about a broad range of patient typologies. Moreover, besides a general reference line, regional equations, accounting for regional differences in mortality rates, were also developed and reported. Peter Suter emphasized in a companion editorial that such a new sophisticated tool should better allow performance assessment within individual ICUs [41]. Afessa et al. [42] studied the impact of missing Acute Physiology Score (APS) values on risk-adjusted mortality rates. In their analysis of more than 38,000 patients, they found that predicted mortality rates were significantly associated with the number and types of missing variables: the more variables were missing, the lower became the predicted mortality rates — which, in turn, leads to falsely increased risk-adjusted mortality rates. This, of course, might be of importance for the assessment of ICU performance.

Soares et al. [43] evaluated the performance of two different comorbidity measures, the ACE-27 and the CCI, in predicting 6-month mortality in a cohort of critically ill cancer patients. Their single-centre study included 772 consecutive patients admitted over a period of 45 months. They found the most frequent comorbidities in their cohort to be hypertension, diabetes mellitus and chronic pulmonary disease. The authors concluded that severe comorbidities should consistently be considered in the assessment of critically ill cancer patients and that the ACE-27 seems to be a useful instrument for this purpose.

Organ dysfunction

Besides the evaluation of the severity of illness, the assessment of organ dysfunction/failure receives increasing interest. Kajdacsy-Balla Amaral et al. [44] evaluated the usefulness of the Sequential Organ Failure Assessment (SOFA) score as a severity marker. They analysed 748 patients from six countries and concluded that the maximum SOFA score, adjusted for age and presence of infection, might be able to predict mortality in this population. Performance, however, was variable between countries, and further studies would be needed to elucidate this issue. Cabré et al. [45] examined the incidence and mortality of multiple organ dysfunction syndrome (MODS) in a Spanish sample of intensive care units. The authors wanted to evaluate if daily measurement of the SOFA could be used for decision-making in patients in whom limitation of life support was to be initiated. They studied 1,340 patients presenting with multi-organ dysfunction, admitted over a 2-month period to 79 ICUs. Besides a high mortality of 45%, the authors found that some type of limitation of life support was applied in a very high percentage of non-survivors. Moreover, patients over 60 years, who exhibited a SOFA score > 9 for at least 5 days, were unlikely to survive. Du Cheyron et al. [46] evaluated outcome and attributable mortality rates of mild and severe acute renal failure (ARF) in critically ill patients with cirrhosis. For this purpose, they matched 41 and 32 patients with mild and severe ARF, respectively, with controls without ARF. Patients with ARF exhibited a higher baseline severity of illness, more often organ failures of the respiratory and cardiovascular system, a longer stay in the ICU, and also significantly increased crude and risk-adjusted hospital mortality rates. Multivariate survival analysis exhibited ARF as the most important predictor for death (Hazards Ratio (HR) 4.1), followed by alcohol abuse, severe sepsis or septic shock. Patients with severe ARF showed significantly increased risk-adjusted mortality, suggesting an excess risk of death attributable to the renal failure. Munnur et al. [47] compared the outcome of critically ill obstetric patients in two different countries: the USA and India. They compared women admitted during pregnancy or up to 6 weeks postpartum, admitted to the ICU. Their study revealed several differences between these two regions: Indian women exhibited a higher severity of illness, a greater incidence of several organ dysfunctions and also more gravidity-associated problems. Not surprisingly, maternal as well as foetal mortality was also strikingly higher in these women (25% vs 2.3% and 13% vs 51%, respectively).

Health services research

Increasing costs of health care systems, and the fact that intensive care medicine makes up a big part of these costs, places increasing pressure on intensivists to prove the efficacy and, moreover, efficiency of their care, in order to identify where and how we could further improve the care of our patients. Azoulay et al. [48] studied incidence of and risk factors for post-ICU mortality in critically ill patients with infection, using data from the European Sepsis Study, which took place in 28 ICUs in eight countries. In this study, 10.4% of patients discharged alive from the ICU died later during the same hospital stay, this being more common among medical patients and patients with hospital-acquired infection or microbiologically documented infection. They reported the main risk factors to be patient characteristics and infection characteristics, severity at ICU admission, as well as persistent organ dysfunction at ICU discharge. From these results they concluded that it would be necessary to further evaluate possible changes in managing these patients, including changes in ICU management, discharge facilities or post-ICU discharge follow-up by intensivists.

To describe discharge practices and physicians' decisions associated with these practices was the objective of the study by Heidegger et al. [49]. They assessed (via a questionnaire) the response to five clinical situations in which a decision about discharge had to be taken. They found a wide variation in discharge decisions and, besides, that discharge decisions might be influenced by institutional factors as well.

Training of intensive care physicians, in order to achieve a common European core competency, has become a major project of the European Society of Intensive Care Medicine (ESICM). With grant help from the European Community, the CoBaTrICE project has been launched. The underlying principle of the project is the concept that a specialist in ICM trained in one country should possess the same core skills and abilities as one trained in another, thereby guaranteeing a common minimum standard of clinical competence. The project will use survey and consensus techniques to develop a web-based programme which should define the core competencies of an ICM specialist and link each competence to relevant assessment criteria and educational resources. The manuscript by Barrett and Bion [50] reports about the first step of the project: a survey undertaken with national

ICM representatives from seven geographical regions. As a major result, considerable variations in the structures and processes of ICM training worldwide were found. Sluiter et al. [32] studied the implementation of multidisciplinary structured work-shift evaluations at a paediatric ICU, in order to enhance team communication. The starting point was that paediatric ICUs worldwide have difficulty recruiting and retaining experienced staff, and a federal action has been demanded to improve this issue. In order to enhance team communication, multidisciplinary structured work-shift evaluations were implemented and the effects of this intervention studied. As a result, almost two-thirds of the staff felt a positive influence of this intervention on team communication. Satisfaction regarding communication with colleagues increased after the intervention (92% vs 76%). Moreover, emotional exhaustion in the PICU team decreased significantly.

Brain injury

Progress in the management of critically ill patients has often come with increased understanding of pathophysiology. The development and availability of new clinical monitors that allow access to more detailed pathophysiology, particularly when the data is available longitudinally throughout the illness, facilitate this aim. In August last year, Thomas Lescot et al. [51] published a paper titled "A quantitative computed tomography assessment of brain weight, volume, and specific gravity in severe head trauma". This paper presented a considerable challenge to the Editorial Board, not least because the results were entirely conflicting with previous data. This group showed, using CT scanning, that after traumatic brain injury the specific gravity of the brain increased. This was associated with a worsening of the patient's injury assessed by neurological exam or Marshall grading of the CT scan. Perceived wisdom is that specific gravity decreases in brain after traumatic injury, due to an influx of water and solutes, cerebral oedema, detectable by magnetic resonance imaging (diffusion weighted imaging) and assessed routinely by measuring the increase in pressure associated with this phenomenon. After debate, the paper was published and was accompanied by an editorial by Professor Nino Stocchetti, who highlighted some of the very important methodological uncertainties associated with using CT-derived data to assess mass, volume and density [52]. The technique has been widely used in lung; however, in lung there is a very wide range in Hounsfield units (300–900 HUs). In brain, the range is very small (4–5 HUs), and this very small range in HUs is determined by a very large number of interlinked variables. Such variables include the composition and, therefore, atomic weight of particles within a particular area of brain, neuronal compression leading to an increase in density and finally the Compton effect (a detailed description of the above is beyond the scope of this year-in-review article; we refer interested readers to Professor Stocchetti's editorial).

Clinicians dealing with severe and moderate traumatic brain injury (TBI) frequently triage referrals because of a limitation in specialised neurological ICU resources. Dr. Hukkelhoven et al. [53] showed that it is difficult to accurately identify patients who will benefit from specialist intensive care unit services based upon baseline demographic characteristics. Referral and admission of all such patients to a centre with specialised neurologic critical services is to be encouraged and is supported by a recent paper in The Lancet by Patel et al. [54]. These papers together support the concept of a neuro-critical care team managing critically ill neurologic patients to improve outcome. Jaffres et al. [55] attempted to stratify risk in moderate and mild traumatic brain injury, using CT scan data and emergency room transcranial Doppler (TCD) measurements. After TCD measurement on both middle cerebral arteries, neurologic outcome was assessed 7 days after the traumatic brain injury. Increased pulsatility index after mild and moderate TBI is associated with further neurological deterioration, and the authors suggest that this investigation could be used to triage patients to a level of care more appropriate for their potential to decline. Clearly, a larger study is required to validate this observation, but this simple investigation at relatively low cost may improve quality of care in the future.

Development of neurophysiological monitoring in the intensive care unit has been a fraught task. Anaesthesia monitors including Bispectral Index (BIS), entropy and now auditory evoked potential monitoring [56] have been used and compared with clinical assessments of sedation scale. There are instances in which clinical assessment is not possible and these include patients receiving neuromuscular blockade, although this practice is less commonly employed. This patient group represents a considerable challenge. Professor Kenny's group showed that a derivative of the auditory evoked potentials were superior when compared with bispectral index and spectral edge frequency 95% [56]. Tim Walsh described the limitations of many of these monitors in his 2004 editorial [57], evoking a need for refinement of filtering of EMG signal.

Luciana Mascia et al. [58], and Peter Andrews in an accompanying editorial [59], assessed the effect of increasing tissue pressure on vascular beds, which could be described as a Starling resistor. Increasing tissue pressure within the lung increased physiological dead space, carbon dioxide tension and intracranial pressure in traumatic brain-injured patients subjected to increasing positive end-expiratory pressure when there was failure of lung recruitment. However, where the patient had lung recruited, tissue pressure increased less and physiological dead space increased less, and intracranial pressure remained stable. The accompanying editorial provocatively suggested that therapeutically manipulating venous pressure within the cerebral circulation might

allow for recruitment of microvasculature collapse due to raised tissue pressure (intracranial pressure) [59]. Such a therapeutic intervention requires a leap of faith and monitoring able to assess regional brain perfusion.

Better understanding of functional genomics and molecular biology will improve our comprehension of many disease processes. Martinez-Lucas examined the relationship between the Arg72Pro polymorphism of p53 and the outcome for patients after traumatic brain injury, showing that the Arg/Arg genotype of the Arg72Pro polymorphism in p53 is associated with a greater chance of poor outcome at discharge from the surgical intensive care unit [60]. The number of patients recruited to the study is relatively small and the results require further substantiation in a large prospective data series. Nakos et al. [61] showed variation in auto-antibodies to lipids in the serum of Guillain-Barré patients in response to the course of the disease. They showed that all patients developed antiphosphatidylinositol antibodies of the IgM family and anti-cardiolipin antibodies of the IgA and IgG families. Importantly, a decrease in the antiphosolipid antibodies was observed after 1 day of treatment with gamma globulin. Two days after the final day of gamma globulin administration, the IgG antibodies increased again, and the authors conclude that, in Guillain-Barre syndrome, there is an extensive immune response which is altered after IgG treatment. They also suggest that monitoring of these other auto-immune antibodies may provide a marker for response to treatment. Laplace et al. [62] examined the serum from patients with severe trauma and haemorrhage and looked at its in vitro reactive oxygen species production in cultured human umbilical vein endothelial cells. The group showed that the serum from these haemorrhagic-shock trauma victims does induce the active oxygen species formation in naive endothelial cells in a way that was correlated with the degree of shock and supports this as a potential mechanism for ischaemia reperfusion of the phenomenon. Minambres looked at serum samples taken from cerebral drainage in brain-injured patients and examined the concept of this inducing apoptosis of lymphoid Jurkat cells in vitro [63]. They noted that, despite being performed on lymphoid cells (which are easier to handle), that the apoptotic effect was increased in patients with a higher mortality and poorer functional recovery.

Thus, this year's sedation and neurologic intensive care papers encompass functional genomics, molecular biology, health care services research and physiological monitoring developments. Whether any of these new pieces of information filter into routine clinical practice will depend on time and the repeatability of observations. However this editorial board remains optimistic about the healthy state of neurologic and sedation research in intensive care.

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