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Paediatrics

Increasingly in paediatric intensive care, as in the adult sphere, the intensivist's focus is increasingly guided towards not only reducing mortality but also to ensuring that survival is morbidity-free. Baghurst et al. [1] reported on the applicability of sequential control charts for monitoring of the quality of paediatric intensive care using risk-adjusted probabilities of death estimated by the Paediatric Index of Mortality version 2 (PIM2). A total of 10,710 patient records submitted to the Australia and New Zealand Paediatric Intensive Care registry from 8 PICU's were used in the report. During the 2-year monitoring period the investigators demonstrated that their methodology was able to detect one 'alarm' for poor PICU performance and one 'alarm' for better than expected PICU performance. In their paper, the authors present a detailed description of sequential analysis methodologies and describe their potential prospective use as tools for monitoring the performance of intensive care units. They caution that 'alarms' for poor or excessively good performance are arbitrarily set and are not necessarily indicative of 'real' problems. Alarms should, however, act as triggers for investigation to ascertain whether the data is sound and if so whether true clinical over or underperformance exists. Numa et al. [2] undertook a study to determine whether outcomes were influenced by time of admission to an Australian tertiary paediatric intensive care unit without 24 h per day in-house intensivist cover. Evening, night and weekend cover by staff intensivists was provided mainly by telephone with discretionary return to hospital to support resident paediatric staff. The authors found that a lack of in-house intensivist was not associated with any increase in risk-adjusted mortality or increased length of stay. They attribute these findings to a combination of relatively experienced junior staff and the effectiveness of telephone backup and discretionary attendance from intensivists after hours. Two studies in 2008 looked at the quality of survival of children after undergoing intensive care. In a case-control study, Elison et al. [3] reported on a detailed neuropsychological follow-up of 16 children, with mean age 9.44 ± 2.85 years, tested a mean of 4.8 ± 1.4 months following hospital discharge. They detected the presence of impaired memory and attention in children following acute illness and links between memory anomalies and emotional/behavioural problems. These findings, if replicated in a larger study, are very important to children and their parents and teachers. Knoester et al. [4] also reported on early neurocognitive sequelae of intensive care but in addition reported information on physical outcomes. They determined that 69% of children had detectable physical sequelae 3 months after PICU discharge. Whilst 30% of sequelae were attributed to previously unknown illness, 39% were acquired of which 8% were related to complications of PICU procedures. Finally, in the area of patient safety and quality, Burmester et al. [5] reported on the apparent benefit of the introduction of a structured prescription education programme and standardised prescription template in a paediatric cardiac ICU. The total number of prescription errors fell from a baseline of 16.8% of prescriptions to 4.8% after the implementation of the measures and this was associated with a small but statistically significant reduction in the incidence of Adverse Drug Events. Weight-based variations in drug dosing are often quoted as a factor in the known high incidence of drug errors in paediatric practice. Disappointingly, tenfold miscalculations which are particularly common and dangerous in children if the decimal point is misplaced during calculations showed no improvement with the studied interventions. This report highlights the need for regular ongoing education in critical care units which typically have high prescription volumes and often see high turnover of staff, particularly 'junior' prescribers such as resident medical staff.

The high mortality of septic shock in children was confirmed in a paper from Wolfler et al. [6] who reported a prospective observational study across 15 Italian paediatric intensive care units conducted over a period of 1 year. During the study 2,741 children were admitted to the participating PICU's. The incidence of severe sepsis was 1.6% and that of septic shock 2.1%, with associated mortalities of 17.7 and 50.8%, respectively. In March 2008 the Journal published a landmark paper from de Oliveira et al. [7]. They studied children with septic shock who were resuscitated according to ACCM/PALS guidelines [8] with or without ScvO2 goal-directed therapy. In this randomised controlled trial, there was a significant difference in mortality rate with use of ACCM/PALS haemodynamic support guidelines for septic shock between patients with or without $ScvO_2$ guided therapy. Patients who received therapies directed to the goal of $ScvO_2 > 70\%$ were given more fluid, red blood cells and inotropic support after the initial resuscitation, with a resulting 3.3-fold reduction in mortality. This study supports the incorporation goal-directed therapy using the endpoint of a $ScvO_2 \geq 70\%$ within ACCM/PALS guidelines the use of which provided a significant beneficial impact on the outcome of children and adolescents with septic shock in this study. Recently the use of vasopressin and vasopressin analogues, potent vasoconstrictors, has been reported in the management of vasodilatory shock in children. Jerath reported a retrospective study of the use of vasopressin in a series of 157 children in a multidisciplinary PICU. Haemodynamics appear to have been favourably influenced, but the authors noted adverse effects on renal function and lower platelet counts associated with vasopressin use. Yildizdas et al. [9] performed a randomised non-blinded

comparison of the use of the vasopressin analogue terlipressin in a group of 58 children with refractory septic shock. Although terlipressin had no beneficial effect on mortality rate in this study, its use was associated with increased mean arterial pressure, improved oxygenation, decreased length of stay in the PICU and had a beneficial effect on survival time among nonsurvivors. Despite these interesting early reports, the place of vasopressin and its analogues in the management of shock states in children is not yet established. Until blinded, randomized, and placebo-controlled studies are conducted in children with septic shock and in other shock states which compare the use of vasopressin-like drugs to standard treatments such as noradrenaline, their use should be considered only a rescue therapy of last resort.

With increased experience, improved surgical techniques, and advances in postoperative care and immunosuppressive therapy, paediatric intestinal transplantation is already into the medical mainstream. In this article, Hauser and coll [10] reviewed the literature on intensive care of paediatric intestinal transplantation as well as their own experience. This article covers the following areas: the indications for intestinal transplantation, the management of critically ill children awaiting intestinal transplantation, the operative procedure, the postoperative management. This last area deals with the intestinal graft, the liver graft, the cardiovascular, respiratory and renal support, the electrolyte and haematologic management, the pain and infection control, the rejection and other alterations in graft function, the nutritional support, the problems of high stomal output, the immunosuppressive treatment, the outcomes and the upcoming challenges. The authors concluded that transplant teams accept patients with higher morbidity and higher risks for complications and indicate that many of these patients would benefit from earlier referral for transplant evaluation before severe complications develop.

Sedation and analgesic practices vary widely in both adult and paediatric intensive care. However, relatively little high quality evidence supports current paediatric practice. Lamas et al. [11] investigated the utility of the bispectral index (BIS), auditory-evoked responses (AEP) and Ramsay and COMFORT clinical scales in the assessment of sedation in critically ill children. Simultaneous recordings were obtained. In children in whom neuromuscular blockade was not being used, correlation between the four methods was moderate or good. However, only BIS and AEP were found to be potentially reliable in those children who were both sedated and subject to neuromuscular blockade. The authors concluded that their results support the finding that the clinical scales do not evaluate the level of sedation accurately in critically ill children with neuromuscular relaxation, leading to a higher risk of over or undersedation. They suggest that in these children, BIS and the AEP index methods may provide a better assessment of the level of sedation. However, they caution that lack of correlation between these two methods in children with neuromuscular relaxation and the absence of a reference method to evaluate sedation in the relaxed patient means that their results must be interpreted carefully. Further studies are needed.

Recently, Akcan-Arikan et al. [12] have described a modified version of the RIFLE criteria for paediatric patients (pRIFLE). Their proposed pRIFLE criteria are based on a decrease in estimated creatinine clearance (eCCL),and urine output is based on body weight. Plötz et al. [13] independently evaluated the pRIFLE criteria in a cohort of 103 children in a European PICU. Sixty children (58%) developed acute kidney injury (AKI) according to pRIFLE criteria of whom six required renal replacement therapy. The authors conclude that pRIFLE criteria may guide the early identification of patients at risk of AKI and therefore guide early initiation of therapy, with potential to avoid progress from 'risk' to injury'. Hoover and colleagues reported a series of 26 children on ECMO for respiratory failure who received CVVH for >24 h and compared these to ECMO/non-CVVH case-matched control children. Significant findings included a faster time to desired caloric intake and reduced furosemide use in CVVH treated children. Although no obvious survival benefit related to use of CVVH was demonstrated, the association of CVVH on ECMO with improved fluid balance and nutritional management was compelling.

Performing optimal cardiovascular monitoring in critically ill children is a considerable challenge. The Journal published four papers in 2008 which address various aspects of this challenging field. Durand et al. [14] investigated whether the measurement of respiratory variations in aortic blood flow velocity (ΔV peak Ao), systolic arterial (Δ SAP) pressure and pulse pressure (Δ PP) could accurately predict fluid responsiveness in ventilated children. Standardised volume challenges were given to 26 children with preserved ventricular function. Aortic blood flow was analysed by transthoracic pulsed Doppler. Whilst a positive correlation was found between ΔV peak Ao and volume expansion-induced gain in stroke volume, measurements of Δ SAP pressure and Δ PP were of little value in predicting responses to fluid augmentation in ventilated children. In a preliminary study, Knirsch et al. [15] compared the measurement of cardiac output using the Ultrasound Cardiac Output Monitor (USCOM) with pulmonary artery catheter-derived thermodilution cardiac output in a group of 24 children undergoing cardiac catheterization. The main finding was that cardiac output measured with USCOM did not reliably represent absolute values measured by pulmonary artery catheter thermodilution, with a mean percentage error higher than 30%. The limitations of transthoracic pulsed Doppler cardiac output measurement in comparison to cardiac output measurement by the

thermodilution technique has been recognized [16]. A number of user-dependent technical factors have been shown to influence ultrasound-derived measurements in other studies in a variety of situations. In addition, possible inaccuracy in algorithm-derived aortic valve diameter used in calculation for cardiac output from flow can introduce systematic error. Many of these limitations are negated if serial measurements are used to derive trends in aortic flow rather algorithm-derived 'absolute' cardiac outputs. Frey et al. [17] brought clarity to the interpretation of aspects of the photoplethysmographic wave which is displayed by most pulse oximeters. They demonstrate that it may be used to derive additional haemodynamic information in some selected situations when, for instance, arterial blood pressure monitoring is not available. The advantages of this method are its widespread use, non-invasiveness and continuity. The authors suggest that haemodynamic deterioration, whether suddenly occurring or slowly evolving over time, may be detected by this method. There is only minimal reference to photoplethysmography monitoring in the paediatric literature.

Three studies published in 2008 relate to aspects of the care of children undergoing cardiac surgery using cardiopulmonary bypass. Tissières et al. [18] described the use of the biomarker n-terminal brain natriuretic peptide (N-proBNP) and troponin I in 20 children following valvular surgery. Their results demonstrated that N-proBNP was superior to troponin I in reflecting clinical and echocardiographic postoperative recovery. Furthermore the authors suggest that preoperative N-proBNP reflected postoperative myocardial functional capacity, thus potentially helping in the early identification of patients who are at risk of chronic cardiac dysfunction. Another biomarker, plasma angiopoetin-2 (Angpt-2), a vascular growth factor, was found by Giuliano et al. [19] to independently predict cardiac ICU length of stay in a series of 48 children palliative or corrective cardiac surgery. The angiopoietins are a family of vascular growth factors that are necessary for both developmental and pathological angiogenesis. ANGPT-2 promotes increased vascular permeability and inflammation and has been shown to be increased in adults with congestive heart failure and the acute coronary syndrome. The authors conclude that ANGPT-2 appears to be an important biomarker of adverse outcome following CPB. Further studies pertaining to the role of angpt-2 in the pathophysiology of capillary leak syndrome following CPB are warranted. At a more practical level, the study reported by Ross-Russell et al. [20] is a large prospective report of the measurement of phrenic nerve latency in 310 children before and after cardiac surgery. Phrenic nerve injury being a relatively common and clinically important complication of cardiothoracic surgery). The authors ascertained an incidence of phrenic nerve injury associated with surgery of 20%. Injury was associated with an increased duration of postoperative ventilation (20 vs. 96 h, $P < 0.001$). Of particular interest in this report is medium term follow-up which shows that one-third children recovered function within 1 months and a further one-third within 3 months.

Two papers recently published in the Journal shed further light on the mechanisms of paediatric respiratory disease. A paper by Plunkett et al. [21] addressed the question of whether the D allele of the I/D polymorphism of the angiotensin converting enzyme (ACE) gene is associated with increased susceptibility to acute hypoxaemic respiratory failure (AHRF) in critically ill children. Previous reports have linked the D allele of the ACE gene to susceptibity for ARDS in critically ill adults and bronchopulmonary dysplasia in pre-term infants. In a single centre prospective study, AHRF developed in 13.9% of 216 critically ill children. There was no significant difference in the frequency of the D allele between patient groups with and without AHRF. The authors suggest that this may suggest differences in the pathogenesis of paediatric AHRF and adult ARDS. Phospholipases A2 is an enzyme widely distributed in the body and was the focus of a report from De Luca et al. [22]. The enzyme is primarily involved in the turnover of membrane phospholipids and lipid digestion. In addition phospholipase A2 is involved in inflammation pathways through the formation of eicosanoids and other inflammatory mediators. In the lungs the secretory form of the enzyme (sPLA2) is produced mainly by alveolar macrophages and secreted into the alveoli. sPLA2 has been shown to be involved in lung inflammation and surfactant degradation and it may play a role for sPLA2 in the development of acute respiratory distress syndrome (ARDS). De Luca et al. provide evidence that sPLA2 is present in high concentrations in bronchoalveolar lavage fluid obtained from neonates with pneumonia and hyaline membrane disease. In this study, sPLA2 levels correlated negatively with dynamic compliance and positively with indices of poorer oxygenation. It appears therefore that the enzyme plays a role in the pathogenesis of respiratory failure in neonates.

Respiratory disease caused by the respiratory syncytial virus (RSV) accounts for almost 10% of admissions to PICU's [23]. RSV disease is characterised by inflammation of the small airways with raised airways resistance, air-trapping and pulmonary consolidation, disproportionately effects young infants due primarily to their poor respiratory muscle reserve. ICM recently published three papers describing different ventilatory strategies for infants with RSV disease. Javouhey et al. [24] used non-invasive ventilation as their primary form of respiratory support in 27 infants. They applied continuous positive airway pressure (CPAP) at 5–10 cm H_2O with additional bi-level positive pressure ventilation of 12–20 cm H_2O as required. Compared to an immediately prior historical cohort of infants with the disease, the intubation rate was significantly lower (52 vs. 89% $P < 0.01$). Berner and

colleagues [25] adopted a different strategy, successfully using high frequency oscillatory ventilation whilst allowing spontaneous breathing in a group of 9 infants with RSV. These two strategies are essentially delivering physiologically similar therapy, maintaining spontaneous ventilation and relying on CPAP to maintain lung volume and reduce the work of breathing. The suggestion that CPAP is clinically effective in RSV bronchiolitis possibly through reduced work of breathing in babies with RSV bronchiolitis was first made by Beasley and Jones [26] in 1981. Whilst Thia et al. [27] have recently confirmed the utility of nasal CPAP in infants with RSV bronchiolitis, showing that they have lower PaCO2 values, Cambonie et al. [28] have finally shown in an elegant study that the use of nasal CPAP rapidly unloads the respiratory muscles, reducing the work of breathing, in young infants with severe RSV bronchiolitis. Argent et al. [29] addressed similar issues in two related papers investigating the mechanics of breathing in children with severe croup and the effect of nebulization of epinephrine on measures of airway obstruction [30]. Respiratory mechanics were studies in 20 infants with severe croup. Patients were found to maintain minute ventilation by means of large increases in mean intrathoracic pressure required to overcome inspiratory flow limitation. Nebulised epinephrine was found to result in short-lived improvement in some but not all patients with croup. Both inspiratory and expiratory airway resistance fell in patients responding to nebulised epinephrine. Oesophageal pressures in both studies were measured via a feeding tube and were found to be satisfactory for quantification of the acute response to nebulised epinephrine whereas flow measurements were unhelpful.

Finally two clinical reports address areas of the management of acute respiratory failure in children where significant differences from adult practice are evident. Pathan et al. [31] reported a series of 124 children categorised as receiving 'paediatric extra-corporeal life support' in a single institution from the inception of their ECLS programme in July 1992 until December 2005. Clinical selection criteria operated during the study were those of severe respiratory failure failing to respond to conventional management and in whom recovery was believed to be reasonably possible. Survival to hospital discharge was 62 with 59% surviving to 1 year. Severity of pulmonary dysfunction pre-ECMO and the presence of shock predicted higher risk of mortality. Kneyber et al. [32] raise the important question of whether we know the true incidence of the acute respiratory distress syndrome in children, or whether it is under-recognised. They retrospectively reviewed 533 mechanically ventilated children admitted to two regional Dutch paediatric ICU's. Chest radiographs were screened for the presence of bilateral infiltrates, PaO2/FiO2 ratios calculated and left ventricular dysfunction ruled out by echocardiography. Forty-one (7.7%) of children met criteria for ARDS giving a population-based incidence of ARDS of 2.2 per 100,000 per year. The incidence of paediatric ARDS is low compared to adults, but the authors suggest that many cases of ARDS are categorised by their underlying diseases such as viral infections, leading to significant underreporting of ARDS. This may be particularly important when planning randomised –controlled trials, as significant underestimation of the effected population could lead to erroneous trial designs or abandonment of trials at the planning stage due to perceived difficulty in recruiting subjects in a timely and cost-effective manner. Bachmann et al. [33] investigated the level of adoption of paediatric ventilation technologies from the participants at two international conferences. The authors used the approach of Rogers' which addresses both differences among individuals and characteristics of the innovation [34]. The authors concluded that whilst evidence of outcomes is the most relevant factor for assessment of potentially beneficial technologies, other factors that encourage adoption of mediocre technologies, or that retard adoption of potentially beneficial technologies, must be understood and acknowledged.

Ethical and legal issues in clinical research

In a concise review, Truog [35] reminds us the specificities and issues in paediatric clinical research. Universal requirements for ethical research are on one hand the respect of subject's autonomy and on the other the protection against harm (the risk-benefit ratio). Respect of autonomy for a child under 18 implies that investigators, whenever possible, seek his–her assent, besides the parental authorization. Protection is achieved via a drastic limitation of the risks children can be exposed during a trial: in the US, the threshold is a "minimal risk" for healthy children and a "minor increase over minimal risk" for diseased ones. Then, Dr Truog proposes a three-step approach of evaluation of paediatric research protocols. The basic concept here is the so-called "component analysis": the research protocol has to be broken in several components, those part of standard care and those which are necessary for research, in addition to care. Each of these components are separately analysed in terms of risk/benefit balance. However, appreciation of "minimal risk" is always debatable, and it is the essential role of the Research Ethics Committee (RECs, or IRBs in the US) to define it on a case to case basis.

Minneci et al. [36] review a few recent randomized clinical trials performed on severely ill patients (the ARMA trial comparing a low and a lage Vt in ARDS, the trial assessing the effect of growth hormone in ICU patients and the TRICC trial, on the level of blood transfusion, also in ICU patients) and emphasise the crucial importance of the control group. They convincingly show

that most of the controversies which followed the publication of some of them stemmed from the inappropriate design of control groups. A well designed control group has two main functions: the first one is to protect the patients enrolled in the trial, and the second is to guarantee the external validity of the conclusions of the research. If the new therapy is to replace the existing standard, it has to have been tested against this standard. Authors' recommendations are that a control group should not be historical, needs to represent current care and should be enrolled along with the new treatment group. Of course, in all large trials involving severely ill patients, a DSMB will monitor safety by comparing the intervention group to this control group. Special difficulties are commonplace in critical care research: patients populations are frequently heterogeneous, syndromes are dealt with, instead of diseases (septic shock, ARDS.), many treatments are delivered with titration: Vt, PEEP, catecholamines, blood transfusion, making the design of a control group extraordinary arduous (one size does no fit all.).

Zamperetti and Latronico [37] give a rather grim view of the regulatory aspects of clinical research in Italy. Basically, directive 2001/20/EC has been literally translated and transposed in the Italian legislation, thus creating a "legal representative", which has not been defined, at the difference of nearly all EU member states. In consequence, decisions for any specific protocols depend on local REC, with no coordination or common guidelines. Similarly, a waived or deferred consent in emergency research may or may not be possible, depending of the local REC, which may base its decision on directive 2001, which prohibits it, or the Oviedo Convention, which makes it possible.

A clear description of the Convention of Human Rights and Biomedicine (Oviedo) of the Council of Europe is provided by Elmar Doppelfeld [38]. The mechanisms by which states and governments, members or not of the EU, sign and ratify the conventions and protocols produced by the Council of Europe are described, as well as the links between the European Commission and the Council (not obvious to all.). Concerning research on severely ill patients (a vulnerable population), special provisions are written in the Additional Protocol. Conditions for waiving consent (emergency) and for designation of surrogate decision-makers in case of incapacity are specified. Research on incompetent persons when no direct benefit is provided is possible, under some specific provisions.

End of life issues

Charles Sprung et al. [39] published in ICM their seventh paper derived from the huge Ethicus database. This study has demonstrated a large gradient from Northern to Southern regions in Europe as to the end of life decisions in ICUs. It was certainly tempting to see whether physician's values could explain these discrepancies. Clearly, the lesser degree of end of life decisions in the South corresponds to more paternalistic views, as expressed by a more frequently cited "unresponsiveness to therapy", a lesser degree of documentation of their decisions and also a lesser consideration for patients' "best interest". However, all investigators, irrespectively of their location, gave a low priority to patient or family request. The authors conclude that ".there is room (in Europe) for greater engagement with patients and their families to promote patient autonomy in the end of life decision-making process"!

End of life decisions are influenced by the religious affiliation of physicians, despite the delimitation of religion from "acculturation" is not always clear-cut. This was another important demonstration by the Ethicus study [40]. Bulöw et al. [41] review the world's major religions' points of view on end of life decisions in the ICU. The Jewish perspective gives a fascinating insight into a new Israeli law which deals with the prohibition by Halacha of withdrawing mechanical ventilation. Surprisingly enough, the Islamic perspective is not far from the catholic tradition (the moral of intention, for instance), but the authors take the precaution to indicate that in different countries, "recognized religious scholars" may have the last word.

"Death rattle" is a common occurrence after "terminal" extubation, at the end of life. It may destabilize families and jeopardize an otherwise well conducted withdrawal of life support in the ICU. Erwin Kompanje et al. [42] provide an excellent overview of the phenomenon and give guidelines on how to prevent and to treat it. This is probably one of the most useful recommendations in a crucial subject, though usually ignored.

The ICM series on national legislations on end of life in ICUs, which started in 2006, continued in 2008 with Austria [43], along with the guidelines produced by the Austrian Association of Intensive Care Medicine [44] and Spain [45].

Cabre et al. [45] have described the legal framework for end of life decision in Spain. As in other European countries, the Spanish society is currently concerned by controversies as to limitation of care in emergency departments or ICUs, a debate obscured by the absence of a clear delimitation between euthanasia and the withdrawal of life support. It is good news to learn that the Court of Justice of Madrid finally cleared the physicians involved in the "Leganés case" [46] from any wrongdoing. A very interesting initiative, which should be replicated elsewhere, is the choice of end of life decisions as an indicator of good quality of care by the Spanish society of critical Care, the SEMICYUC.

Servillo and Striano [47] tell us how in Italy, as in Spain, end-of-life care gives fierce debates, further enhanced by the strong influence of the Catholic Church in such matters. Dr Riccio, an anaesthetist involved in the Welby case has also been relaxed by justice. The debate is now focused on the introduction in the Italian law of "advanced directives". As in other countries where laws are mute on end of life decisions, the role of professional societies (the SIAARTI in Italy) is crucial in guiding physicians and in protecting them occasionally.

Outcome research and critical care organization

Sexual dysfunction seems to be highly prevalent not only in the community, but also after critical illness. Although patients report sexual function to be important, symptoms of sexual dysfunction after major illness are seldom evaluated by medical practitioners. Ulvik et al. [48] thus studied sexual dysfunction in trauma patients 3–8 years after discharge from the ICU, using a questionnaire. The cohort comprised of 325 consecutive trauma patients over 18 years of age admitted to their ICU in the period 1998–2003, of which 210 were eligible. The response rate was with 74% highly satisfactory. Patients were asked to describe their sexual life both, prior to the ICU admission and presently. Half of the patients reported sexual function to be unchanged, 41% impaired, and 9% even to be better than before the trauma. Erectile dysfunction was found to contribute in 27% of men younger than 40 years and 51% of men 40 years or older. Age, being single, Injury Severity Score, and depression were associated with a poor sexual function. The authors concluded that due to the high incidence and also the possible impact on individual quality of life, sexual function should be regularly evaluated at least in trauma patients.

The SAPS 3 risk-adjustment system, developed from a world-wide multicenter study, has been published in 2005. As for all severity of illness systems, external validation studies are needed to proof the prognostic performance in settings different than the one the score has been developed from. Ledoux et al. [49] undertook a prospective study in their institution to evaluate the performance of SAPS 3 and to compare it to two other systems, namely APACHE II and SAPS II. They included 802 consecutively to the ICU admitted patients over an 8-month period. With respect to discrimination, APACHE II performed worse than SAPS II and SAPS 3 models. Calibration was unsatisfactory again for APACHE II and for the general SAPS 3 model, whereas it was satisfactory for SAPS II and the SAPS 3 model with the Central European equation. The authors concluded, that the SAPS 3 admission score and its model for Central and Western Europe was more discriminative and better calibrated than APACHE II, but it was not significantly better than the SAPS II. Since this study presents as a single centre study with a low patient number, the results have to be viewed with caution. Multicenter studies with higher patient numbers are required to determine the prognostic ability of a risk-adjustment system.

Intra-abdominal hypertension (IAH) has only in the past decade received attention as a potential source of problems for critically ill patients. Several recent studies have highlighted the possible impact of increased intra-abdominal pressure on renal function. Dalfino et al. [50] studied the relationship between IAH and acute renal failure (ARF) in critically ill patients. They included all patients who were consecutively admitted during a 6-month period. IAH was defined as a IAP $>=$ 12 mmHg in at least two consecutive measurements performed at 24-h intervals. ARF was defined according to the failure class of the RIFLE criteria. Almost a third of their patients developed IAH. ARF developed in 19% of their patients, with a significant difference between the two groups: 43.2% in the IAH versus 8.1% in the non-IAH group ($P < 0.05$). Shock and low abdominal perfusion pressure were predictive factors for the development of ARF. A cut-off point of 12 mmHg had the best predictive power for the development of ARF. Although raw hospital mortality was significantly higher in patients with IAH, risk-adjusted mortality rate was not different between the two groups. The authors concluded, that IAH is clearly an independent and strong predictor for the development of ARF. However, the contribution of impaired systemic hemodynamics should also be taken into account.

The impact on mortality of early coagulation disorders after severe burn injury was addressed by Lavrentieva et al. [51]. In this single centre prospective study conducted on 45 patients with severe thermal burn injury the 28-day mortality rate was 33%. The presence of overt DIC was related to mortality (OR = 0.1). Antithrombin, protein S, plasminogen activator inhibitor 1, and SOFA score on day 3, protein C on day 5, and thrombin/antithrombin complexes on day 7 revealed a good prognostic value for ICU mortality. The authors concluded that the severe thermal injury is associated with the early activation of coagulation cascade, presence of DIC, organ failure, and increased mortality.

Bedside adherence to clinical practice guidelines may influence the outcome. The dissemination of medical knowledge is essential and practice surveys are important to assess practices of health-care professionals and develop strategies for more effective actions.

The TECLA study [52] with a multicenter, 1-day cross-sectional design assessed adherence to clinical recommendations for three interventions routinely used in critical care medicine. A total of 419 patients hospitalized in the 44 participating ICUs in 4 countries were enrolled. Red blood cell transfusion ($n = 29$) was performed appropriately in 22 patients (76%), while among the 390 patients who received no transfusion 4 (1%) had a valid indication.

Setting of tidal volume in acute respiratory distress syndrome, assessed in 45 patients, was deemed appropriate in 37 cases (82%). Prescription of stress ulcer prophylaxis ($n = 128$) was appropriate in only 24 patients (19%), while among the 268 patients who were not treated 28 (10%) had an indication. The survey concluded that the implementation of recommendations varies across different domains of care, being suboptimal in some contexts.

Wheeler et al. [53] carried out an audit to quantify the variability in the concentration of drug infusions prepared in an adult intensive care unit. They also established whether there was a relationship between the quality of syringe labelling and drug preparation. They collected 149 discarded syringes containing midazolam, insulin, norepinephrine, dopamine, potassium or magnesium. Residual solutions were sampled, concentrations were measured, and syringe labels were awarded a score for labelling quality based on an 11-point scale. The majority of the infusions differed from the expected concentration by more than 10%. Magnesium infusions were least likely to be properly labelled. There was a positive correlation between quality of syringe labelling and drug preparation. After the introduction of a new electrolyte prescription chart, magnesium and potassium preparation significantly improved but there was still substantial variability. The authors conclude by a plea for the use of pre-prepared syringes or standardized drug preparation and labelling systems.

Scientific societies have published position papers recommending certain critical care pharmacy activities. In a brief report LeBlanc et al. [54] described the activities of international pharmacists who had a significant portion of their duties dedicated to critical care to increase the awareness of pharmacist roles to the critical care team. The authors analyzed data obtained in a website based survey. The majority of respondents (74.4% of a total of 168 pharmacists) attended medical rounds and 54.8% were involved in research. The majority of pharmacists (72.6%) were involved in drug monitoring (mainly aminoglycosides and vancomycin). A few prepared intravenous medications or total parenteral nutrition, 13 and 8.4%, respectively. Authors conclude that critical care pharmacists participate in a wide range of activities and they expect that the involvement of the pharmacist in critical care teams will increase.

In a prospective multicentre study, Takala et al. [55] tested the feasibility of three software-driven critical care protocols. They applied software-driven protocols for cardiovascular management, sedation, and weaning during the first 7 ICU-days in 174 cardiac surgery and 41 septic patients. Protocol use was discontinued in 12% of patients by the treating clinician and in 6% for technical/administrative reasons. This study advocates that multiple software-driven treatment protocols can be simultaneously applied with high acceptance and rapid achievement of primary treatment goals (Initial hemodynamic stability, Sedation targets, Weaning time).

In a prospective observational study, Perren et al. [56] assessed whether cross-checking of the physician ICU transfer report by ICU nurses may reduce transfer report errors. About 123 patients were randomly selected at discharge from the ICU and physician ICU transfer reports were cross-checked by nurses using defined review criteria. About 76 (62%) transfer reports were affected by at least one error which was classified as simple (81%), serious (14%) or critical (5%). Thirty-five (28%) transfer reports were considered potentially harmful. Among 305 intercepted errors, 247 were prescription errors (26% of all prescriptions), 45 involved proposed procedures, and 13 were deficient in updating diagnoses. Only the number of medications included in the transfer report was associated with the occurrence of at least one critical/serious error.

Calzavacca et al. [57] identified risk factors for mortality in 228 patients receiving one or more Medical Emergency Team reviews during daytime hours over a 1-year-period. Delayed Medical Emergency Team activation and not-for resuscitation orders were the only factors that showed an independent association with mortality.

Ospina et al. [58] in a comprehensive literature review analysed which monitoring techniques have been shown to improve outcomes in ICU patients, concluding that there is no broad evidence that any form of monitoring improves outcomes in the ICU. Through an highly sensitive search in the Cochrane Central Register of Controlled Trials (CENTRAL) and MedLine, for prospective, randomized controlled trials (RCTs) conducted in adult patients in the ICU and the operating room (major surgical procedures), the authors focused on the impact of monitoring on outcome. Of 4,175 potential articles, 67 evaluated the impact of monitoring. Forty studies were related to hemodynamic monitoring, 17 to respiratory monitoring, and 10 to neurological monitoring. Positive non-mortality outcomes were observed in 17 of 40 hemodynamic studies, 11 of 17 respiratory, and in all 10 neurological studies. Mortality was evaluated in 31 hemodynamic studies, but a beneficial impact was demonstrated in only 10. For respiratory monitoring, seven studies evaluated mortality, but only three of them showed an improved outcome.

Clinicians–family interactions and nurse's burnout

In a qualitative study, Mc Adam et al. [59] described the contributions to care that 25 family members perform while their loved one is at high risk of dying in the ICU. Interviews with relatives were recorded and three independent raters coded transcripts. Work roles that family members take on while their loved one is in the ICU consisted of active presence, patient protector, facilitator, historian, coach, and voluntary caregiver. These multiple roles performed by relatives are often

not valued or go unrecognized by ICU health care providers.

Giannini et al. [60] investigated visiting policies in 257 Italian ICUs. Median daily visiting time was 60 min and 55% of ICUs had one daily visiting slot. There were restrictions on number (92% of units) and type (17%) of visitors and on child visits (69%). Policies were not modified for child patients in 9% of ICUs, nor for a dying patient in 21%. No waiting room was provided by 25% of ICUs. Gowning procedures were required for visitors in 95% of units. In 66% of ICUs informative material on the unit was provided to the family on patient admission. Regional area and volume of admissions significantly influenced visiting hours. One-third of ICUs were being rethinking their policies.

Verdon et al. [61] evaluated the level of burnout in 97 members of the nursing team. 28% showed a high level of burnout. Among concerns reported by the nurses, only the lack of patients' co-operation, the organization of the service and the rapid patient turnover were independently associated with a high level of burnout.

Sedation and pharmacology

Weinert and Sprenkle [62] assessed the impact of sedative exposure on ICU recall and symptoms of posttraumatic stress disorder in patients receiving mechanical ventilation. They interviewed 149 patients who required >36 h of mechanical ventilation 2 months after ICU discharge. Eighty patients were also interviewed at 6 months. ICU recall was greater for events occurring at the end of critical illness; however, 18% of subjects had amnesia for the entire ICU course. Posttraumatic stress disorder prevalence was 17% at 2 months and 15% at 6 months. Recall of a delirious memory during critical illness was associated with more severe posttraumatic stress symptoms. Neither ICU recall nor posttraumatic stress symptoms were associated with the intensity of sedative administration during mechanical ventilation. Posttraumatic stress symptoms were lowest in patients either the most awake during mechanical ventilation or the least awake. In a prospective, randomised, single-blinded, controlled study, Röhm et al. [63] compared sevoflurane and propofol in terms of recovery times from sedation. A total of 70 patients after elective coronary artery bypass graft surgery received either sevoflurane ($n = 35$) or propofol ($n = 35$) for short-term postoperative sedation in the ICU. Mean extubation times from termination of sedation (the primary outcome) were significantly shorter with sevoflurane than with propofol (22 vs. 151 min). The length of ICU stay was comparable in both groups, but hospital length of stay was significantly shorter in the sevoflurane group. Costs for sedation per patient were similar in both groups. Suchyta et al. [64] compared mortality and discharge disposition in critically ill patients with and without drug or alcohol dependence and patients with and without psychiatric disorders. They found that patients with drug or alcohol dependence were at higher risk for ICU admission compared to the general population. However, the prevalence of psychiatric disorders was significantly lower than in the general population. Drug or alcohol dependence predicted shorter hospital length of stay. In a retrospective review of patient records over 2 years in 20 French city hospitals Lapostolle et al. [65] evaluated 838 patients with an elevated serum digitalis concentration (digoxin > 1.95 ng/ml or digitoxin > 23 ng/ml), following chronic or acute exposure. Of these, 67 (8%) had received antidotal therapy with Fab fragments. Five independent factors were associated with the use of antidotal therapy: acute overdose (OR 15.74), Fab fragment availability in the hospital (11.06), serum potassium (1.81), and heart rate (0.96). Mortality was significantly lower in Fab-treated (6%, 4/67) than untreated patients (15%, 117/770). The authors concluded that antidotal therapy is underused in patients with an elevated digitalis concentration and the use of identical criteria for antidotal treatment after acute and chronic poisoning should help optimize outcomes.

Miscellanea

Vandijck et al. [67] compared characteristics and outcomes in ICU-patients with haematological malignancies and severe sepsis/septic shock who had or had not received recent intravenous chemotherapy. Among the 186 patients, there were 77 patients with severe sepsis and 109 with septic shock; 91 (49%) had received recent intravenous chemotherapy. In-hospital, and 6-month mortality rates were 45.1 versus 58.9%, and 50.5 versus 63.2% in patients with and without recent chemotherapy, respectively. By multivariate analysis, previous chemotherapy was protective. After adjustment with a propensity score for recent chemotherapy, chemotherapy was not associated with outcome.

In a review article [66] on organ dysfunction in hemophagocytic lymphohistiocytosis Créput et al. provides an overall overview on this entity and aims at helping clinicians to maintain a high level of suspicion regarding the diagnosis. The parts covered in this review are: the clinical and laboratory features, the cytology and histology aspects, the etiologies, the pathophysiology, the prognosis and mortality, and the therapeutic approach. The authors concluded that the management of the hemophagocytic lymphohistiocytosis requires a multidisciplinary team, and the high mortality in patients with no etiological diagnosis requires aggressive investigation and treatment.

Payen et al. [68] assessed blood leucocytes gene profiling in the course of the septic shock recovery period

and tested the relation between encoding gene expression and protein level in 17 septic shock patients. Gene expression levels were studied on a dedicated microarray of 340 genes involved in inflammatory processes. The time-related gene expression study showed significant changes in ten genes. Among them, S100A8 and S100A12 had a reduced expression over time compared with D0, whereas CD74's expression increased. By RT-qPCR, the S100A8 plasma levels decrease in parallel with the gene expression decrease. The CD74 gene expression evolution significantly correlated with HLA-DR monocyte expression.

In a fascinating mini-series Foresti et al. [69] and Bauer et al. [70] reviewed the role and pathophysiological mechanisms of the heme oxygenase–carbon monoxide system (HO–CO) and the challenging potential use of CO as therapeutic agent. In the past decade, the use of CO gas in pre-clinical experimental models of disease has produced some remarkable data indicating that its therapeutic delivery to mammals could alleviate inflammatory processes and cardiovascular disorders. However, the inherent toxic nature of CO cannot be ignored, knowing that inhalation of uncontrolled amounts of this gas can ultimately lead to serious systemic complications and neuronal derangements. From a clinical perspective, a key question is whether a safe and therapeutically effective threshold of CO can be reached locally in organs and tissues without delivering potentially toxic amounts through the lung. The advent of CO-releasing molecules (CO-RMs), a group of compounds capable of carrying and liberating controlled quantities of CO in cellular systems, could be a plausible alternative in the attempt to overcome the limitations of CO gas. Although in its infancy and far from being used for clinical applications, the CO-RMs technology is supported by very encouraging biological results.

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