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Year in review in Intensive Care Medicine 2014: II. ARDS, airway management, ventilation, adjuvants in sepsis, hepatic failure, symptoms assessment and management, palliative care and support for families, prognostication, organ donation, outcome, organisation and research methodology

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Acute respiratory distress syndrome

Prognosis of ARDS is not only related to physiological alterations and therapeutic strategies but to the underlying disease. Patients with malignancies and ARDS have received less attention. Outcomes were studied in a huge cohort of more than 1,000 patients with mainly haematological malignancies and infection-induced ARDS [1]. The most important point was that survival improved over time. The authors outlined the fact that non-invasive ventilation was used in 30 % of the patients but failed in 70 % of these. An important point corroborating epidemiological studies done in other categories of patients with acute respiratory failure was that non-invasive ventilation failure was associated with a worse outcome.

The use of chest computed tomography is sometimes limited by the repetitive exposure to radiation. In a comparative study including 45 ARDS patients, reducing radiation by 70 % did not alter quantitative and visual anatomical analysis [2].

Recruitment manoeuvres still represent a controversial issue in the symptomatic treatment of hypoxaemia in ARDS. A systematic review and meta-analysis [3] including ten randomised clinical trials (RCTs) reported a reduction in hospital mortality by the use of recruitment manoeuvres. However the quality of evidence was judged to be low because of the risk of bias in the included studies and the fact that other therapeutic strategies were concomitantly used. The use of recruitment manoeuvres in ARDS patients is still a matter of debate.

The exact mechanisms explaining how prone positioning improves gas exchange and, more importantly, patient outcome in ARDS are largely unknown. Prone position exerts various beneficial effects regarding the ventilation–perfusion relationship. In a detailed review Guerin et al. [4] described the proposed beneficial mechanisms in ARDS patients, making the point that prevention of ventilator-induced lung injury and improvement in haemodynamics likely contribute. There are several hypotheses to explain the discrepancies observed in the literature such as the enrolment of mild or moderate ARDS patients in some trials. In a meta-analysis [5] the authors stratified seven trials on prone positioning in ARDS on the basis of high or low tidal volumes. Prone positioning was associated with a significant decrease in the relative risk of death only in studies using low baseline tidal volume ($\leq$8 ml/kg PBW). This meta-analysis suggested that tidal volume is a potential confounding factor in interpreting the results of prone position trials in ARDS.

Another important issue about prone positioning is a benefit–risk balance of potential adverse effects. In an ancillary study of the PROSEVA trial [6], it was shown that the rate of pressure ulcers was higher in the patients who were positioned prone vs. controls, in particular those ulcers involving the face and the anterior part of the thorax. The use of prone positioning, male gender, higher age, body mass index and SAPS II score at admission were all independently associated with the risk of developing a pressure ulcer. This study clearly suggested that the use of prone positioning should be done according to well-defined medical and nursing protocols in each ICU using this technique.

In a review paper, Pinsky [7] summarized the effects of PEEP on right ventricular function. A rapid increase in central venous pressure while right ventricular systolic volume does not increase suggests that right ventricular failure is present. Lung-protective strategies aimed at decreasing lung overdistension favourably impact right ventricle performance. Under these circumstances right ventricular dysfunction remains associated with a worse outcome. Inhaled nitric oxide (iNO) may reduce right ventricular afterload, but the use of iNO remains controversial in ARDS patients. Despite being effective in improving oxygenation in some patients, all trials have concluded that iNO does not improve the outcome of ARDS patients, and impaired renal function may be a side effect. However, as stressed in a review [8], there is the need to evaluate the use of iNO during lung-protective ventilation as a rescue therapy prior to ECMO when mechanical ventilation and prone positioning have failed to improve gas exchange.

An important issue regarding ECMO use in ARDS patients is the need to develop useful tools to select patients who could benefit. Indeed, the development of mobile units is associated with extra costs and it is of upmost importance to correctly predict the outcome on the basis of easily obtainable parameters. The most recent scores were detailed and compared in a review [9, 10]. ECMO initiation after more than 7 days of mechanical ventilation and the presence of extra-pulmonary organ dysfunction are consistently associated with poorer outcome. There is, however, a need to validate these scores in studies including patients from ICUs worldwide.

Airway management, ventilation and sedation

Mosier and Law [11] updated recent findings about airway management in critically ill patients. They highlighted the importance of pre-intubation evaluation for potential difficulty [12] and appropriate planning and implementation of guidelines [13], positioning, pre-oxygenation [13] and, in selected patients, the use of a neuromuscular blocking agent have been shown to be useful for minimizing the difficult intubation and intubation-related complications [13]. Although there are controversies regarding the use of video laryngoscopy as the primary method of intubation, it has been shown to be at least as good as, and often more successful than, direct laryngoscopy [14, 15].

De Jong et al. [15] systematically reviewed and meta-analysed RCTs and prospective [14] and retrospective observational studies of video laryngoscope vs. direct laryngoscope (DL) in adults who were intubated in the ICU. Nine trials with a total of 2,133 participants (1,066 in VL and 1,067 in DL) were included in the analysis. Compared to direct laryngoscopy, video laryngoscope reduced the risk of difficult intubation [OR 0.29 (95 % confidence interval (CI) 0.20–0.44)], Cormack grade 3/4 [0.26 (0.17–0.41)], oesophageal intubation [0.14 (0.02–0.81)] and increased the first-attempt success rate [2.1 (1.4–3.2)]. No statistically significant differences were found for severe hypoxaemia, cardiovascular collapse or airway injury.

Graciano et al. [16] evaluated the incidence and associated risk factors of difficult tracheal intubations in paediatric ICU. They used data collected prospectively from 15 paediatric ICUs related to tracheal intubation for the National Emergency Airway Registry for Children (NEAR4KIDS). A total of 1,516 oral tracheal intubations were reported (median 2 years of age) and 97 % of patients were intubated with direct laryngoscopy. Difficult tracheal intubation was reported in 9 % of intubations and was associated with a higher incidence of oxygen desaturation less than 80 % (48 vs. 15 %, $p < 0.001$), adverse tracheal intubation-associated events (53 vs. 20 %, $p < 0.001$) and severe tracheal intubation-associated events (13 vs. 6 %, $p = 0.003$). A history of difficult airways and sign of upper airway obstruction were associated with difficult tracheal intubation.

Serpa Neto et al. [17] performed an individual patient data meta-analysis of seven studies (2,184 patients) to assess the associations between tidal volume size, duration of mechanical ventilation and need of sedation in patients without ARDS. Patients were assigned to three groups based on tidal volume size ($\leq$6, 6–10 and $\geq$10 ml/kg PBW). The number of patients breathing without assistance by day 28 was higher in the group ventilated with tidal volume $\leq$6 ml/kg PBW as compared to those ventilated with tidal volume $\geq$10 ml/kg PBW (93 vs. 89 %; $p = 0.03$). Only two studies (187 patients) could be included in the meta-analysis of need of sedation. There were no differences in number of days patients received sedatives, opioids or neuromuscular blocking agents, or in the total dose of any of these drugs. The results suggest that use of lower tidal volumes in patients without ARDS at the onset of mechanical ventilation could be associated with shorter duration of ventilation. Use of lower tidal volumes seems not to affect sedation or analgesia needs, but this need to be confirmed in a robust well-powered RCT.

Negative pressure pulmonary oedema may be more common in ICU patients than is thought. Ventilation with low tidal volume in patients with increased respiratory drive may lead to patient–ventilator asynchrony that causes increased breathing effort and the generation of high negative inspiratory pressures that will further worsen pulmonary oedema [17].

Non-invasive ventilation

In 2014, studies assessed the use of non-invasive ventilation (NIV) in medical [18, 19] and surgical [20, 21] patients. Lorut et al. [22] reported a large multicentre RCT that investigated whether systematic postoperative NIV vs. standard care prevented respiratory complications following lung resection in a selected population of 349 COPD patients. NIV was delivered intermittently through facial or nasal masks 6 h per day for 48 h postoperatively. The rates of acute respiratory events (primary endpoint) or acute respiratory failure were not different between the NIV and control group. Rescue NIV was used less in the NIV group, but re-intubation rates were not different between the groups. Mortality rates were low in both groups. This paper was accompanied by an editorial [23], which gave some possible explanations for the lack of beneficial effects. In the postoperative period, it is sometimes difficult to clearly separate "preventive" and "curative" application of NIV. Probably some of the patients received NIV for "grey zone" indications (at the time of starting NIV and also after) which may be considered as an intermediary state between "preventive" and "curative" application of NIV [23]. Further studies are needed to better identify the patients who may benefit from NIV after thoracic surgery and the optimal NIV protocol (duration, settings, interfaces and humidification systems use for gas conditioning).

Lellouche et al. [24] assessed the impact of the type of humidification system used on the success rate of NIV using ICU ventilators for ARF in an RCT. This international RCT included 247 patients, 128 of whom were allocated to a heat and moisture exchanger (HME) group and 119 to a heated humidifier (HH) group. There was no significant difference in the intubation rates (the primary endpoint) between the HH and HME groups (37 vs. 30 %, respectively, $p = 0.28$). No significant difference was observed for NIV duration, ICU and hospital LOS or ICU mortality. In addition, no difference in the patients' mucosal dryness was reported with HH in comparison with HME. These results suggest that despite a strong physiologic rationale supporting the use of HH during NIV [25], this method cannot be recommended as a first-line treatment in all patients with ARF. The use of an HME (ideally with a low dead space) while removing the additional dead space (flex-tubing) seems to be acceptable in light of the results of this study. Finally, contrary to recommendations published in 2012 that propose HH for NIV rather than HME, the authors found no difference in outcomes. However, in the presence of persistent high $PaCO_2$ levels associated with threatening encephalopathy, the reduction of dead space with an HH may be

considered. This paper was accompanied by an editorial [26] which asked the question why a trial that finished enrolling patients in December 2003 would be published 10 years later. The authors of this editorial [26] emphasized that every reasonable attempt should still be made to publish the data.

Brambilla et al. [19] evaluated the efficacy of non-invasive continuous positive airway pressure (CPAP) to improve outcomes in severe hypoxaemic ARF (hARF) due to pneumonia in an RCT conducted in four Italian centres. Patients were randomised to receive helmet CPAP (CPAP group, $n = 40$) or oxygen delivered with a Venturi mask (control group, $n = 41$). Helmet CPAP reduced the risk of reaching criteria for endotracheal intubation (the primary endpoint) as compared to oxygen therapy (6/40 = 15 % vs. 26/41 = 63 %, respectively, $p < 0.001$). The CPAP group also showed faster and greater improvement in oxygenation in comparison to controls. In either study group, no relevant adverse events were detected; two patients were intubated in the CPAP group and one in the control group.

Schnell et al. [18] evaluated the use and outcomes of NIV over a 15-year period (1997–2011) from a multicentre database of critically ill patients who required ventilatory support for ARF. The impact of first-line NIV on 60-day mortality was evaluated using a marginal structural model. Of 3,163 patients, 1,232 (39 %) patients received NIV. Over the study period, use of first-line NIV increased from 29 to 42 % and NIV success rates increased from 69 to 84 %. NIV decreased 60-day mortality, and this was observed mainly in patients with acute-on-chronic respiratory failure, but not in patients with cardiogenic pulmonary oedema, or in patients with hARF (both immunocompetent and immunocompromised). NIV failure was an independent, time-dependent risk factor for mortality. The authors emphasized that further studies are warranted on early predictors of NIV failure to help in selecting patients for NIV [27, 28].

Weaning

In their "Our paper 20 years later" Frutos-Vivar and Esteban described how withdrawal from mechanical ventilation has changed. At the beginning of the 1990s, there was little evidence regarding the best method of withdrawing patients from mechanical ventilation. Today, withdrawal from mechanical ventilation (or weaning) is one of the most common procedures in ICU. Esteban et al. [29] published one of the seminal papers on weaning in which they reported that the best method for withdrawal from mechanical ventilation in difficult-to-wean patients was a once-daily spontaneous breathing trial with a T-piece. Following this study [29, 30], several other studies [31] have shaped weaning as an evidence-based technique. The results of these studies [29, 32] have been applied progressively to clinical practice. Currently, the withdrawal from mechanical ventilation could be summarized as the performance of a spontaneous breathing trial to evaluate extubation readiness (this trial could be performed with a T-piece, which occurs most commonly, or with CPAP or low levels of pressure support). Most patients could be disconnected after passing the first spontaneous breathing trial. In patients who failed the first attempt at withdrawal, the use of a once-daily spontaneous breathing trial or a gradual reduction in pressure support is the preferred weaning method. However, new applications of the standard techniques, such as NIV, or new methods of mechanical ventilation, such as automatic tube compensation, automated closed-loop systems and automated knowledge-based weaning systems could play a role in the management of the patients with difficult or prolonged weaning. In the future, studies should better evaluate the relationship between the implementation of protocols for the optimization of sedation and weaning outcomes. Moreover, the focus should be on the relationship between ICU-acquired weakness and weaning failure. An early mobilization of patients could be proposed for the prevention or early therapy of ICU-acquired weakness associated with mechanical ventilation weaning-sedation protocols.

Adjuvants in sepsis

The use of statins in sepsis is very controversial. Recent evidence suggests that there is no indication for using statins either in infection or ARDS in ICU patients. The dose and the potency of statins could be important factors. In a cohort study including more than 50,000 patients from Taiwan [33], a propensity score-based analysis concluded that the use of high-potency statins ($\geq$10 mg rosuvastatin, $\geq$20 mg atorvastatin, $\geq$40 mg simvastatin) was associated with reduced 1-year mortality as compared to non-statin users and low-potency statin users.

Recombinant human IL-7 (rhIL-7) may be a potential therapeutic intervention for sepsis. Investigators have demonstrated that rhIL-7 has beneficial effects both in terms of mortality and immune dysfunction in mice models [34] and restoring sepsis-induced human lymphocyte functions to a normal response in an ex vivo study [35]. Demaret et al. [36] evaluated the association of soluble plasmatic levels of CD127 (sCD127), an IL-7 receptor, and mortality in 70 septic patients. They demonstrated that sCD127 levels were independently associated with mortality and could discriminate survivors from non-survivors (area under ROC curve = 0.85).

Ulinastatin is a serine protease inhibitor that inhibits several pro-inflammatory proteases and decreases inflammatory cytokine levels and mortality in experimental sepsis. In a pilot trial ($n = 114$), intravenous ulinastatin

was associated with reduced organ failures and mortality in patients with severe sepsis [37].

The long-term outcomes were reported from the 6S trial on HES 130/0.42 vs. Ringer's acetate in 804 patients with severe sepsis. Mortality rates at 1 year did not differ between the two intervention groups, but a clinically relevant decrease in mortality with starch could be rejected [38].

A computer decision support system (CDSS) facilitating blood glucose control has been suggested to improve the outcome of ICU patients through tighter control. A randomised trial of 2,684 ICU patients failed to show improved outcome in patients managed with a CDSS vs. control. Moreover use of CDSS was associated with more events of severe hypoglycaemia [39].

The gastrointestinal tract is pivotal in regulating insulin secretion and glycaemia. It is now understood that the incretin effect is due to two hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones may have therapeutic potential by lowering blood glucose and reducing glycaemic variability with no risk of hypoglycaemia, which may be of particular benefit in the critically ill [40].

Hepatic failure

'Acute-on-chronic' liver failure has high infection rates, which are associated with mortality. A proposed model implies that the markedly increased risk of infection is due to systemic translocation of microbes from the gut, impaired hepatic clearance mechanisms and decreased ability of circulating immune cells to combat infectious cues (peripheral immune-paresis) [41].

New knowledge also advances our understanding of the pathophysiology of acute liver failure (ALF). ALF causes massive "spillover" of cytokines to the circulation causing SIRS in the initiation/propagation phase and compensatory anti-inflammatory response (CARS) thereafter. Persistent CARS response is linked to recurrent infections complicating ALF, conferring a poor prognosis. SIRS and CARS further affect other organ systems, e.g. circulating inflammatory mediators crossing the blood–brain barrier and they induce encephalopathy/cerebral oedema through microglial activation [42].

Larsen and Wendon [43] reviewed the recent literature on paracetamol-induced liver toxicity, one of the most frequent causes of acute liver failure worldwide. In addition to severe liver dysfunction, the patients often have shock, lactic acidosis, kidney injury, coagulopathy and encephalopathy. Drug toxicity profile as well as pathophysiological mechanisms were reviewed. The treatment of paracetamol-induced liver toxicity consists of *N*-acetylcysteine and supportive care in the ICU, but there are only few randomised trials of its management. Liver transplantation, including supportive care with albumin dialysis and plasma exchange, should be considered in the most severely ill patients.

Symptoms assessment and management

An essential task for ICU staff is to acknowledge and relieve physical and emotional suffering in patients and their relatives. Schmidt et al. [44] performed a comprehensive review on dyspnoea, an unrecognized or at least underestimated suffering in mechanically ventilated patients. The prevalence of dyspnoea varied between 11 and 100 % among the eight prospective studies included. Mechanically ventilated patients qualified the sensation of dyspnoea as "moderate to intense" and it could even reach unbearable levels necessitating the administration of analgesics according to some studies. Dyspnoea was also associated with anxiety and delayed psychological sequelae such as recollections of ICU experiences and post-traumatic stress disorder (PTSD), all important deleterious consequences; consequently, we must keep in mind that dyspnoea can often simply be improved by altering ventilator settings. The authors concluded that future studies are needed to better delineate the impact of dyspnoea in ICU and to define diagnostics, monitoring and therapeutic protocols.

PTSD also appears to be common among ICU survivors, and symptoms of PTSD can persist for many months after recovery from critical illness. Long et al. [45] created a conceptual model that integrates know risk factors and current evidence regarding potential strategies to reduce symptoms of PTSD. Until reliable and validated screening tools are developed, clinicians should be aware of the potential modifiable and non-modifiable risk factors that are associated with PTSD among ICU survivors.

Puntillo et al. [46] conducted a single-blinded, randomised trial in three ICUs testing a bundle targeting thirst intensity, thirst distress and dry mouth, which are among the most pervasive, intense, distressful symptoms among ICU patients. A total of 252 cognitively intact patients reporting thirst intensity and thirst distress were randomised to the thirst bundle or usual care. A research nurse administered a thirst bundle that included oral swab wipes, sterile ice cold water sprays and a lip moisturizer for patients in the intervention group. Another research nurse, blinded to group assignment, obtained pre- and post-procedure thirst scores. The simple, inexpensive thirst bundle significantly decreased ICU patients' thirst and dry mouth as compared to the usual care group.

Roulin and Ramelet [47] conducted a study in brain-injured ICU patients to describe their behaviour during rest, a non-nociceptive procedure (calling and shaking shoulders) and a nociceptive procedure (turning the patient).

Patients with absence of movement or those with reflexive flexion or extension responses to a nociceptive stimulus displayed more behaviour during turning than patients with localized responses or patients able to self-report their pain. Face flushing, clenched teeth, clenched fist and tremor were more frequent in patients with stereotyped responses to a nociceptive stimulus. The reliability of their checklist was high and the internal consistency was acceptable. Discriminant and concurrent validity was also supported. This study suggests that brain-injured patients react significantly more during a nociceptive stimulus and the number of observed behaviours was higher in patients with a stereotyped response.

Pressure ulcers are frequent in ICU patients and are associated with adverse outcome and increased costs. A strategy aimed at increasing repositioning frequency (every 2 vs. 4 h) in patients undergoing mechanical ventilation did not, however, reduce the incidence of pressure ulcers in a recent randomised trial [48].

Palliative care and support for families

Relieving physical and emotional suffering becomes particularly important at end of life. On behalf of the Interdisciplinary Advisory Board of the Improving Palliative Care in the ICU (IPAL-ICU) project, Puntillo et al. [49] performed a comprehensive review on palliative care in the ICU focusing on assessing and relieving pain, dyspnea and thirst. Evidence-based methods to assess pain are the enlarged 0–10 numeric rating scales (NRS) for ICU patients able to self-report and the critical care pain observation tool or Behaviour Pain Scale for patients who cannot report symptoms verbally or non-verbally. These validated scales and the relationship between pain, anxiety and fear were further explored in a "What's new in intensive care" article by Gélinas et al. [50]. The Respiratory Distress Observation Scale is the only known behavioural scale for assessment of dyspnoea, and thirst is evaluated by patient self-reporting using a 0–10 NRS. Optimally titrated opioids remain the mainstay for pain management while dyspnoea should be treated by optimizing the underlying etiological condition, patient positioning and sometimes supplemental oxygen. Finally several oral interventions are recommended by Puntillo et al. [49] to alleviate thirst. The authors insist that the quality of care should be monitored in order to improve the assessment and management of these important symptoms.

Long et al. [51] hypothesized that the quality of end-of-life care for patients admitted to the ICU from the hospital ward was lower than that observed among patients admitted from the emergency department (ED). They conducted a cohort study of patients with an underlying chronic illness who developed acute respiratory failure and subsequently died in the ICU in one of 14 hospitals. They compared the family satisfaction with care and quality of dying as assessed by the family and the ICU nurses, as well as quality of palliative care assessed from the medical record. Admission from the hospital ward was associated with lower family ratings of quality of dying and satisfaction than admission from the ED. Interestingly, nurses did not report differences in quality of dying. In addition, patients admitted to the ICU from hospital wards were less likely to have family conferences or discussion of prognosis in the first 72 h after ICU admission, but were more likely to have life support withdrawn. The authors conclude that admission from the hospital ward is associated with family perceptions of lower quality of dying and less satisfaction with ICU care. Differences in receipt of palliative care suggest that family of patients from the hospital wards receive less information.

Sleepiness and fatigue are commonly reported by family members of ICU patients and sleep deprivation causes cognitive deficits. Verceles et al. [52] published a multicentre, cross-sectional survey of family members of patients admitted to ICUs at three hospitals. Family members of ICU patients were evaluated using the Epworth Sleepiness Scale, a standard survey assessing sleepiness, and the Functional Outcomes of Sleep Questionnaire-10, which quantifies the impact of sleepiness on daily activities. They assessed 225 family members and 50 % had Epworth scores consistent with excessive daytime sleepiness and they experienced greater impairment in performing daily activities. This study suggests that half of the family members of ICU patients suffer from excessive daytime sleepiness and that this sleepiness is associated with functional impairment.

In a "What's new" article, Giannini et al. [53] address the issue of limitations on family visits in the ICU. In the past few years several consensus groups have recommended liberal visiting policies in ICU. Nevertheless, these recommendations have not significantly influenced clinical practice in many countries. The authors argue that by welcoming families and visitors in ICU we, as ICU doctors and nurses, are not making a concession to the patient or family, but instead we are recognizing the rights of the patient. The authors make a compelling argument that by opening our ICUs for family visits, we can make a difference for patients and families. The complex and highly technological environment of the ICU can and should become a welcoming place, which respects the needs of patients and families, and where "humanity has a high priority".

In a commentary, Curtis et al. [54] identify some examples of words or phrases in the English language that are commonly used in communicating with patients, families and colleagues and which the authors believe can convey unintended negative messages or which can be confusing to those with whom we are communicating.

Terms such as withdrawing care can imply that clinicians will no longer care for or about patients and their families. Instead, clinicians should talk about "withdrawing life-sustaining treatments". These and other examples provide suggestions for clinicians in using words to be sure that their true intentions are understood.

Jabre et al. [55] investigated the incidence of late psychological burden among family members systematically given the option to witness CPR of a relative as compared with those not routinely offered the option in a cluster-randomized trial in France. The study nicely demonstrated that the proportions of family members experiencing symptoms related to PTSD (32 vs. 20 %, $p = 0.01$), major depressive episodes (31 vs. 23 %, $p = 0.02$) and complicated grief (36 vs. 21 %, $p = 0.005$) were significantly higher in the control vs. the intervention group. Similar results were observed among family members to whom physicians did not propose the opportunity to witness resuscitation.

Prognostication

While of course saving lives is clearly the heart of our mission, we should not forget that good ICU practice starts with appropriate triage decisions. Prognostic indicators associated with long-term outcomes from large multicentre cohorts may help us in making such decisions. Wang et al. [56] identified predictors of 1-year mortality among 493 ALI/ARDS hospital survivors admitted between 2006 and 2010 in multiple units at the Vanderbilt University Medical Center. Mortality increased from 24 % at hospital discharge to 41 % at 1 year. Patients who died after discharge were older and more likely to have been discharged to a nursing home, another hospital or hospice as compared to those who survived to 1 year. Important predictors of mortality were age, comorbidities such as HIV, metastatic and non-metastatic cancer, hematologic malignancy and chronic kidney disease present at the time of admission and not living at home prior to admission. The authors concluded that 1-year mortality is essentially affected by non-modifiable factors and that therefore these factors should be taken into account when testing new interventions in ARDS and improving guidance in the offering of full resuscitation for high-risk patients and in the discussions of prognosis with the relatives.

That critically ill patients with solid cancer have worse prognosis than critically ill patients without any comorbidity is rather straightforward. Puxty et al. [57] performed a systematic review on survival in ICU patients with solid cancer. They identified 35 and 31 studies reporting ICU and hospital survival representing a total sample of 25,339 and 74,061 patients, respectively. The average ICU and hospital mortality was 31 % (95 % CI 24–39 %) and 38 % (34–43 %), respectively, the latter ranging from 5 to 77 %. Worse functional status and severity of illness scores and invasive mechanical ventilation were associated with increased mortality.

Another important factor beside age and underlying comorbidities is frailty. Le Maguet et al. [58] assessed the prevalence and impact of frailty on ICU and 6-month mortality in 196 patients aged at least 65 years admitted across four French hospitals between November 2011 and May 2012. Frailty was defined as either a clinical frailty score ≥ 3 or a frailty phenotype ≥ 5. Of the 46 patients fulfilling the first or both definitions of frailty only 30 % were still alive at 6 months as compared to about 75 % of 42 patients fulfilling the second definition only or the 108 patients without frailty ($p < 0.01$). Frailty was an independent predictor of 6-month mortality after adjustment for classical confounders. Although comorbidities, older age, frailty and not living at home prior to admission alone could not fully discriminate between long-term survivors and non-survivors, these studies indicate that these factors should be taken into account during triage discussions with the patient, relatives and attending physicians.

Besides differences in ventilator strategies, differences in triage decisions among many other confounders may explain the differences in outcome observed across ICUs in the UK with low vs. high volume mechanically ventilated admissions. In a retrospective study of 120,293 adult patients admitted between 2008 and 2010 in 193 ICUs, Shahin et al. [59] found a significant relationship between annual volume and hospital mortality ($p < 0.02$). They found a strong interaction between annual volume and admission type, with a more pronounced volume outcome relationship for non-surgical admission ($p < 0.001$). The interaction between annual volume and initial severity of respiratory failure was not statistically significant. These findings were, however, sensitive to the modelling used.

The management and outcomes of human immunodeficiency virus (HIV)-infected patients have changed dramatically over the two last decades. However, information in the setting of critical illness requiring ICU admission occurring in these patients is scarce and mostly restricted to single-centre studies. Barbier et al. [60] evaluated 6,373 consecutive patients admitted to 34 French ICUs over a 12-year period using the CUB-Réa Database. They observed significant changes in patients' profiles and outcomes over time. Patients admitted more recently were older, had more co-morbidities and were more frequently on mechanical ventilation (MV) and renal replacement therapy (RRT). Overall use of MV and RRT and ICU and hospital mortality rates decreased significantly over time. Delayed ICU admission (>24 h) was associated with increased mortality (OR 1.7, 95 % CI

1.2–2.5). Interestingly, most of the HIV-related complications were not associated with worse outcomes.

In subgroup analyses of the Target Temperature Management trial, mortality did not differ between patients with shock after out of hospital cardiac arrest managed to a target temperature of 33 vs. 36 °C for 24 h [61]. However, cardiovascular failure was more pronounced after randomisation in the patients cooled to 33°C.

Organ donation

Lesieur et al. [62] conducted an observational study designed to assess the theoretical eligibility as organ donors of patients dying in French ICUs after a decision to withhold or withdraw life-sustaining therapy. They collected data on patients admitted to 43 ICUs who qualified for withholding or withdrawing life-sustaining therapy. The theoretical organ donor eligibility of deceased patients was determined by medical criteria for graft selection and according measures withheld or withdrawn and the impact on time to death. A total of 5,589 patients were admitted to the ICU, of which 777 (14 %) patients underwent withholding or withdrawing of life-sustaining therapy. Of the 557 patients who died after a foreseeable circulatory arrest, 278 patients (50 %) presented a contraindication to organ retrieval; 279 patients would have been eligible as organ donors. Yet, cardiopulmonary support was withdrawn in only 154 of these patients, 70 of whom died within 120 min of the withdrawal. Brain-injured patients accounted for 29 % of all patients who underwent withholding or withdrawal of life-sustaining therapy and 57 % of those died within 120 min of the withdrawal. The authors concluded that a significant number of patients who died in French ICUs after a decision to withhold or withdraw life support would have been eligible for organ donation. They also found that brain-injured patients were more likely to die in circumstances which would have been compatible with organ donation.

In a "What's new" article, the Shaw and Elger [63] made the case that, used properly, persuasion can be a supportive mechanism to counsel family members to allow organ donation without unethical coercion. It can be ethical, the authors argued, to use persuasion to help families deal with the stress of a decision to permit donation. Doing so may allow us to respect patients' autonomy when they have expressed support for organ donation. The authors pointed out that families asked about this decision should be given the information relevant to their decision; if the deceased was a registered donor, they should be provided this information. If families may be unaware of the potential benefits of donation, these benefits should be described. The authors argued that if family members offer inconsequential or inaccurate reasons to forego organ donation, they should be persuaded of the problems or inaccuracies of such reasons. Furthermore, they also argue that family members should be informed that many families who refuse consent for organ donation ultimately come to regret that decision. Others have suggested that families' decisions regarding donation should not be challenged as they are distressed over the loss of a loved one, but the authors argued that to compound their difficulty with decision-making by withholding key information is to disrespect the family and patient.

Outcomes

As patient-centred care brings a new focus to short- and longer-term outcomes, there is increasing interest in which measures are most informative and integrative. Using the 6MWD as the main comparator, Denehy et al. [64] analysed how other activity-based measures serve as proxies. The study sample consisted of 177 ICU survivors recruited from acute care hospitals in Australia and the USA. The authors showed good correlation between the 6MWT and the time up and go test, the Berg balance scale and the 5× sit to stand test. The 6MWT explained 54 and 33 % of the variance in the physical part of SF-36 and no clinical variables were significant predictors. 6MWT is one important integrative outcome measure but is of limited utility in those patients unable to walk or severely disabled after critical illness. Choice of outcome measures should be aligned with the study question and capture global disability.

ECMO is a scarce resource and risk stratification for outcome is important and a key issue when patients are retrieved from referral centres. Roch et al. [65] sought to identify patient factors that were associated with unfavourable early outcome in patients retrieved and offered ECMO. Based on a multivariable logistic regression model, a risk score including age, SOFA score and influenza pneumonia, was constructed. The probability of hospital mortality following ECMO initiation was 40 % in the 0–2 score class and 93 % in 3–4 score class with increased age and SOFA score associated with increased risk and a diagnosis of influenza protective of death in hospital. These simple criteria may help to inform bedside decision-making during retrieval for ECMO. Single-centre data and the homogeneity of admitting diagnosis (CAP and influenza) limit the generalizability of these findings.

Functional disability and cognitive impairment after critical illness have been well described. Some gains have been made in the application of post-ICU physical, occupational and cognitive therapy interventions. However, cognitive therapy protocols for administration during the

ICU have not been evaluated. In a feasibility study, Brummel et al. [66] randomised 87 medical and surgical ICU patients with respiratory failure or shock to three groups: usual care, early once-daily physical therapy or early once-daily physical therapy plus a novel twice-daily cognitive therapy protocol. These authors showed that administration of complex multi-modality ICU-based interventions had good compliance and was feasible. There were no differences in cognitive, functional or HRQoL outcomes at 3 months but the study was not powered to determine efficacy for the intervention. This work shows the crucial importance of investing in early pilot work to inform issues related to compliance, feasibility, safety, choice of optimal outcome measures and refinement of sample size and statistical power calculations.

A poignant contribution by Laghi et al. [67] was part of the unique *Intensive Care Medicine* series titled "My paper 20 years later" in which content experts are invited to discuss a more historical work in the context of the current literature and the importance and implications of their early observations. In 1995, these authors published a seminal paper in the *Journal of Applied Physiology* in which they assessed the time course of recovery from diaphragmatic fatigue. They described the persistence of significant fatigue—defined as an effort-induced decrease in muscle contractility that recovers after rest—at 24 h after induction in healthy volunteers. This landmark observation became the tenet of the once-daily, T-tube trial arm in RCTs for ventilator weaning in the ICU and helped to inform the design of a trial of weaning for tracheostomy patients requiring prolonged mechanical ventilation. Further, this work elucidated low-frequency fatigue and the introduction of twitch airway pressure to document the prevalence and outcome of respiratory muscle weakness. These authors rightly assert that there remains a pivotal role for basic physiology studies as part of the spectrum of research that continues to inform practice in mechanical ventilation and the care of critically ill patients.

Organisation

The literature is sparse on supply of acute care services in low-income settings. Such information is essential to guide investments in infrastructure and services to meet the burden of acute diseases, particularly in large urban centres. To address this gap, Austin et al. [68] assessed the acute care services supply (hospitals, hospital beds, ICU beds, ambulances) in seven cities of diverse economic background in Europe, Africa, Asia and North and South America. They demonstrated that there were large variations in the supply of acute care services, which correlated only in part with the countries' gross domestic product. However, some measures of supply (e.g. hospital beds, self-defined ICU beds) were comparable in high- and upper-middle-income cities. Another important finding was that such information frequently is not easily available from governments, with potential implications for future planning, particularly in middle-income countries as these are facing the largest population growth projections.

Quality improvement programs focusing on early recognition and adherence to best practices are the key to improving quality of care and outcomes in patients with sepsis. In this context, Noritomi et al. [69] reported the results on the implementation of a multifaceted quality improvement program (including screening strategies, multidisciplinary educational sessions, case management and continuous performance assessment) in a private network of 10 hospitals in Brazil using a pre- and post-intervention study design. They evaluated the approach in 2,120 patients with severe sepsis or septic shock, and demonstrated significant increases in the compliance to the resuscitation bundle of the Surviving Sepsis Campaign (13 vs. 62 %, $p < 0.001$) and hospital survival (45 vs. 74 %, $p < 0.001$) in the "post-interventional" period. More importantly, the strategy proved to be cost-effective. The results of this study may be of particular relevance for emerging countries where sepsis mortality rates remain disproportionally high [70].

Adequate prophylaxis is essential to prevent venous thromboembolic disease (VTE) in ICU patients, particularly in those at high risk. The PROF-ETEV study evaluated current practices regarding the appropriateness of prophylactic measures in relation to the patients' risk for VTE in 777 patients admitted to several ICUs in Spain [71]. The vast majority of patients had multiple risk factors for VTE and 83 % were at very high risk. Nevertheless, prophylaxis was inappropriate in 23 % of medical, 71 % of surgical and 70 % of major trauma patients according to guidelines criteria. This study reinforces that improvements should be enhanced regarding identification of patients at risk and implementation of appropriate preventive protocols.

The identification of patients at increased risk of delirium is paramount to optimize the implementation of preventive strategies. In a multinational study involving 1,824 patients, van den Boogaard et al. performed a recalibration of PRE-DELIRIC, a delirium prediction model for ICU patients [72]. Despite differences in the studied predictors among the centres, PRE-DELIRIC had good discriminative ability (area under ROC curve 0.77, 95 % CI 0.74–0.79). The authors concluded that subsequent validation studies of the PRE-DELIRIC model are needed as this instrument may aid both the implementation of strategies to prevent delirium and improvements in delirium management of ICU patients.

Grimaldi et al. [73] investigated whether the number and the time course of circulating innate-like T lymphocytes correlated with the development of ICU-acquired infections in critically ill patients, with a particular focus

on the recently identified innate-like mucosal-associated invariant T (MAIT) lymphocytes. Innate-like lymphocytes lie between innate and adaptive immunity and comprise B and T cells characterized by the recurrent expression of antigen receptors with limited diversities. Of note, MAIT lymphocytes display specific reactivity to non-streptococcal bacteria. In this study, the authors observed a significant early decrease in patients with severe bacterial infections compared to both non-infected critically ill patients and healthy control subjects. Conversely, NKT and γδ T cell (other forms of innate-like lymphocytes) counts did not differ among patients groups. Moreover, non-streptococcal bacterial infection was independently associated with the decrease in MAIT cell count, and patients with persistent MAIT cell depletion had higher incidence of ICU-acquired infections.

Van Vliet et al. [74] used the Dutch National Intensive Care Evaluation (NICE) registry to study 1,741 haematological patients requiring ICU admission in more than 90 % of ICUs in the Netherlands between 2004 and 2012. They reported average yearly decreases of 7 % in the risk-adjusted mortality rates for both overall medical admissions and among haematological patients, in parallel with an increase in the proportion of admissions of haematological patients over time. This contemporary study also reinforced that leukopenia was not associated with worse outcomes in these patients.

Research methodology

Several papers were published that can help us in better analysing and reporting study results. Alberti and Boulkedid [75] focused on how to describe ICU data with tables. Beside relatively straightforward recommendations about the type and presentation of tables, the authors elaborate on much more important points for investigators and readers such as determining appropriate measures of central tendency and variability depending on the nature of the variable (quantitative or qualitative variables, ratios), effects size and inferential statistics, indication of the denominators including in the setting of missing data, specifying the appropriate arithmetic precision for quantities, checking the total counts and percentages within categories of variables and the internal coherence of numbers/counts in the text, tables and figures among many other issues.

Beyersman et al. [76] discussed how to measure and report incidences in ICU populations. Incidence of events occurring during ICU stay is typically calculated as the incidence proportion (number of events/number of patients) or as incidence rate (number of incident events/patients days). The latter may be preferred because it accounts for the patient-time at risk. However, this automatically implies that one has to consider also the risks of observing competing events during ICU stay. For instance ICU infections may not be observed as a result of prior discharge from the unit. Similarly, death secondary to infection or any other life-threatening event may not be observed during ICU stay because of discharge from the unit. In order not to present incomplete or misleading results the authors recommend that investigators should always calculate and report the incidence rates of such competing events.

Labarère et al. [77] provided a comprehensive narrative but detailed overview on how to derive and validate clinical prediction models before implementing them into clinical practice. With the help of a 19-item checklist they elaborate on (1) how to retrieve a derivation sample from the original population in order to build an initial model with good performance and internal validity, (2) how to update and improve the model's performance through external validation and (3) how to test the additional value of the predictive model as compared to standard of care at the bedside by performing an impact analysis.

Rochwerg et al. [78] draw our attention to how appropriately estimated and reported (average) effects sizes retrieved from observational or randomised trials should be implemented (at the individual level) at the bedside. Although the quality of evidence based on the GRADE rules and the balance between desirable and undesirable effects are of course primordial to take account in clinical practice guidelines, the authors convincingly argue that no recommendation should trump common sense or strongly held personal belief and that cost and resource allocation should also be taken into consideration.

A systematic review found that non-registration (or registration after trial completion) was common in RCTs of critically ill patients. Moreover, among registered trials, important protocol changes were often made between trial commencement and publication. This identifies and quantifies serious—but correctable—problems for RCTs in critically ill patients [79]. Along this line, scepticism is needed whenever research accomplishments are too good to be true. The distinction between fraud, questionable research practices, extravagant statistics and academic misery can be subtle. False extravagant results are probably far more likely to arise from selective analysis and outcome reporting and data dredging rather than by fraud [80].

Appropriate interpretation of new results requires awareness of emerging methodological issues. An understanding of the proper use of envelopes for randomisation, appropriate covariate adjustment and the need to impute missing baseline prognostic variables will help clinicians identify trials that are less likely to report false positive and/or false negative results [81].

In a "What's new" article, Kompanje et al. [82] reviewed medical research and data protection in the European Union (EU) by the Clinical Trial Directive 2001/20/EC and proposed changes to this directive. In

most EU countries, prior consent by a legal representative is used as a substitute for informed patient consent for non-urgent medical research. Deferred consent by the patient or surrogate decision-maker is accepted as a substitute in acute emergency research in approximately half of the EU countries. In 12 countries, emergency research is not covered in national law. A proposal for a regulation by the European Commission was recently examined by the European Parliament and the Council with the goal of replacing Directive 2001/20/EC. In this proposal deferred patient and/or proxy consent is allowed, but it does not support emergency research. For example, in this proposal deferred consent is only possible when legal representatives are not available. This proposal will delay inclusion of patients in acute life-threatening conditions in short time frames. As the proposal would be binding in all member states, emergency research in acute situations would be impaired by this proposal. Kompanje et al. reviewed this proposal and some alternatives that would better support clinical research in emergency situations.

Conflicts of interest None.

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