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Elie Azoulay
Giuseppe Citerio
Jan Bakker
Matteo Bassetti
Dominique Benoit
Maurizio Cecconi
J. Randall Curtis
Glenn Hernandez
Margaret Herridge
Samir Jaber
Michael Joannidis
Laurent Papazian
Mark Peters
Pierre Singer
Martin Smith
Marcio Soares
Antoni Torres
Antoine Vieillard-Baron
Jean-François Timsit

Year in review in Intensive Care Medicine 2013: II. Sedation, invasive and noninvasive ventilation, airways, ARDS, ECMO, family satisfaction, end-of-life care, organ donation, informed consent, safety, hematological issues in critically ill patients

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E. Azoulay (✉)
Faculté de medicine, AP-HP, Hôpital Saint-Louis, Medical ICU, Université Paris-Diderot, Sorbonne Paris-Cité, 1 avenue Claude Vellefaux, 75010 Paris, France
e-mail: elie.azoulay@sls.aphp.fr
Tel.: +33-1-42499421
Fax: +33-1-42499426

J. Bakker
Erasmus University Medical Center, Rotterdam, The Netherlands

M. Bassetti
Azienda Ospedaliera Universitaria Santa Maria della Misericordia, Udine, Italy

D. Benoit
Ghent University Hospital, Ghent, Belgium

M. Cecconi
St George's Hospital, London, UK

J. R. Curtis
Harborview Medical Center, University of Washington, Seattle, WA, USA

G. Hernandez
Pontificia Universidad Católica, Santiago de Chile, Chile

M. Herridge
University of Toronto, Toronto, Canada

S. Jaber
Saint Eloi University Hospital, Montpellier, France

M. Joannidis
Medical University, Innsbruck, Austria

L. Papazian
Hôpital Nord, Marseille, France

M. Peters
Great Ormond St Hospital, London, UK

P. Singer
Beilinson Hospital, Tel Aviv, Israel

M. Smith
University College London Hospitals, London, UK

M. Soares
D'Or Institute for Research and Education, Rio de Janeiro, Brazil

A. Torres
Hospital Clinic, University of Barcelona, Ciberes, IDIBAPS, Barcelona, Spain

A. Vieillard-Baron
Hôpital Ambroise Paré, Paris, France

G. Citerio
Neurointensive Care Unit, Department of Anaesthesia and Critical Care, Ospedale San Gerardo, Monza, Italy

J.-F. Timsit
APHP-Hopital Bichat, Réanimation Medicale et des maladies infectieuses, Université Paris Diderot, Paris, France

Sedation

Intensive Care Medicine has taken part this year in the ongoing controversy about sedation strategies for the critically ill. Shehabi et al. [1] replicated the ANZ SPICE study design in 11 Malaysian ICUs to assess whether early sedation depth was independently associated with delayed extubation and increased mortality. They

performed a prospective multicenter study that included 259 medical/surgical patients who were sedated and ventilated for at least 24 h. Deep sedation, defined as Richmond Agitation Sedation Score (RASS) ≤ -3, occurred in 71 % of patients at first assessment. Multivariable Cox proportional hazard regression analysis adjusting for confounders confirmed that early deep sedation was independently associated with longer time to extubation, hospital and 180-day mortality. Delirium occurred in 114 (44 %) of patients but was not associated with sedation length upon first assessment. The performance and the feasibility of an automated administration of sedation were evaluated in a phase II randomized controlled trial (RCT) by Le Guen et al. [2]. Thirty-one patients were allocated to receive either propofol or remifentanil, through either an automated or a manual system. In the two groups, targeted bispectral index (BIS) values were between 40 and 60. Propofol consumption was reduced by 50 % in the automated group with a median change of infusion rates of 39 ± 9 times per hour compared to only 2 ± 1 propofol dose changes per hour in the manual group. Similarly, the median number of changes in infusion rates was 40 ± 9 for remifentanil in the automated group, compared to 1 ± 1 dose changes per hour in the manual group. In a single-center pilot study of critically ill patients in spontaneous ventilation undergoing flexible fiberoptic bronchoscopy, the safety and efficacy of sedation with remifentanil target-controlled infusion (Remi-TCI) were assessed by Chalumeau-Lemoine et al. [3]. The procedure was successful, comfortable, and safe in all patients. Patients reported low level of pain and good satisfaction with the procedure.

Delirium prevention has become of paramount importance in the critically ill. Zaal et al. [4] examined the effect of the ICU environment on delirium occurrence. Their ICU recently moved to a new location and was restructured to provide patients with individual rooms, improvements in daylight exposure, and noise reduction. Using a before-and-after study design, they evaluated the effects of the environmental changes in the delirium occurrence during the ICU stay. Although the incidence of delirium remained comparable, delirium duration (adjusted for confounding) decreased by 0.4 days (95 % CI 0.1–0.7).

There is increasing evidence that there is important neuropsychological dysfunction after admission to the ICU. Wolters et al. [5] evaluated the literature from January 1980 to July 2012 to systematically describe the published literature reporting neurocognitive outcomes after critical illness. Studies in adults and with a minimum of 2-month follow-up after ICU were included and the results from 19 papers that met inclusion were reported. The majority of studies reported that ICU admission or episodes of critical illness are associated with some degree of cognitive dysfunction. The reported range of cognitive disability ranged from 4 to 62 % over a follow-up period of 2–156 months. Important limitations included heterogeneity of study samples, differential surveillance and reporting of cognitive outcome, and no uniformity in defining neurocognitive dysfunction.

Weaning and automatic ventilation modes

Perren and Brochard contributed a review article highlighting that efficient weaning requires appropriate sedation policies, fluid balance as well as an individualized approach to understand and treat the failing patients [6].

IntelliVent®, a fully automated mode of ventilation, includes two closed loops: (1) a closed loop designed to keep end-tidal CO_2 ($EtCO_2$) in a defined range by adjusting target minute ventilation (MV) based on input from the user and measured parameters (ASV-CO_2 algorithm) and (2) a closed loop for oxygenation to adjust positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FiO_2) based on oxygen saturation (SpO_2) targets. In a bench test study, Sulemanji et al. [7] evaluated the closed loop modes in simulated clinical scenarios [normal lungs, chronic obstructive pulmonary disease (COPS), acute respiratory distress syndrome (ARDS), and brain injury]. The authors reported that the minor differences observed were in favor of the closed loop modes. Lellouche et al. [8] evaluated the safety of IntelliVent® in an RCT including 60 ICU patients after cardiac surgery. They compared IntelliVent® to the standard of care of ventilation. The percentage of time within the predefined zones of optimal, acceptable, and not acceptable ventilation were 12, 81, and 7 %, respectively, with the standard of care of ventilation, and 89.5, 10, and 0.5 % with IntelliVent® ($p < 0.001$). The authors concluded that IntelliVent® was safe in hemodynamically stable patients immediately following cardiac surgery. In addition to a reduction in the number of interventions, the IntelliVent® system maintained patients within a predefined target range of optimal ventilation.

In a randomized crossover physiological study, Alexopoulou et al. [9] evaluated non-sedated patients (86 % COPD) who received alternating 4-h periods of pressure support ventilation (PSV) and proportional assist ventilation with load-adjustable gain factors (PAV+) equally distributed during the day and night. The authors studied patient–ventilator asynchrony and sleep quality. This trial confirmed previous findings showing that critically ill patients exhibit disorganized and poor-quality sleep and excessive sleep fragmentation. Also, no improvement in sleep quality was observed despite less patient–ventilator asynchrony in PAV+ compared to PSV. The authors concluded that their results do not support the hypothesis that patient–ventilator synchrony plays a central role in

determining sleep quality in these patients. Last, Blankman et al. [10] compared the effect of varying levels of assist during PSV and neurally adjusted ventilatory assist (NAVA) on the aeration of the dependent and non-dependent lung regions by means of electrical impedance tomography (EIT). NAVA ventilation had a beneficial effect on the ventilation of the dependent lung region and showed less over-assistance compared to PSV at the same pressure in the ten mechanically ventilated patients with acute lung injury (ALI).

Noninvasive and invasive mechanical ventilation, tracheostomy, airways

In 2013, the journal has dedicated a large amount of space to noninvasive ventilation (NIV) in various settings. Chiumello et al. [11] investigated whether NIV could be useful in the management of acute respiratory failure (ARF) due to chest trauma in comparison to standard therapy. Ten studies (368 patients) were included in the meta-analysis, including five studies (219 patients) that reported mortality. The results were quite homogeneous across the studies. The summary relative risk for patients treated with NIV compared with standard care [oxygen therapy and invasive mechanical ventilation (IMV)] was 0.26 (0.09–0.71, $p = 0.003$). NIV significantly increased arterial oxygenation and was associated with a significant reduction in intubation rate, as well as in the incidence of overall complications and infections. The increasingly popular NIV can be provided with an increasing range of new equipment, both ventilators and interfaces. Although it has been suggested that the helmet is one of the optimal interfaces, its high compliance—such that it behaves like a damper interposed between the patient and the ventilator—leads to weakening and delay in the inspiratory pressure support. Mojoli et al. [12] performed a series of bench tests to evaluate the effects of increased PEEP (5–10 cmH_2O) and PSV (10–20 cmH_2O) levels. They also evaluated the effects of two additional adjustments aiming to improve the mechanical performance of helmets: inflation of an internal cushion and major reduction of the ventilator circuit resistance. In addition, in a clinical study they collected pressurization and depressurization rates, MV, and patient–ventilator interactions during conventional versus "optimized" set-up (PEEP increased to 10 cmH_2O, low resistance circuit, and cushion inflated). The authors concluded that the mechanical performance of the helmet interface for NIV can be greatly improved by specific adjustments of the ventilator settings, ventilator circuit, and the helmet itself. The bench study confirmed the known favorable effect of increasing PEEP and showed for the first time the advantages associated with inflation of the helmet internal cushion and with major reduction in the ventilator circuit resistance. Each of these adjustments had an independent favorable effect on the speed of inspiratory pressure rise and expiratory pressure drop within the helmet, thus increasing the ventilatory action on the respiratory system obtained by a given pressure support level. The clinical study confirmed that a combination of these adjustments greatly improved the speed of pressure rise and drops within the helmet, and interestingly showed a major improvement in patient–ventilator interaction, with easier triggering and a major reduction in the frequency of unassisted efforts. In a mixed bench and clinical study, Richard et al. [13] showed that despite identical ventilator settings, the different pressure-preset ventilation (PPV) modes lead to substantial differences in tidal volume (VT), transpulmonary pressure (PTP), and breathing variability in the presence spontaneous efforts. This possible harmful effect of i-synchronization, especially when high VT is undesirable, needs to highlighted.

Although pressure-preset NIV is able to compensate for unintentional leaks better than volume-preset NIV, a constant VT may not be guaranteed in the presence of changes in respiratory impedance. To overcome this problem, a volume-guaranteed mode has recently been introduced in most dedicated NIV ventilators or bi-level ventilators both in double-limb and in single-limb circuits (SLC). A study by Fauroux et al. [14] reported that, in the presence of modifications of respiratory impedance, volume-guaranteed ventilation was able to guarantee a preset volume. Conversely, the volume guaranteed was not always ensured in the presence of unintentional leaks. However, ventilators with double-limb circuits or SLC with a true expiratory valve ("non-vented") or with an intentional leak ("vented") were used indifferently. Along this line, Carlucci et al. [15] performed a bench study that focussed on the differences in leak compensation between a "vented" or a "non-vented" SLC configuration. Using an experimental model consisting of a mannequin connected to an active lung simulator, for each level of leak (15, 25, and 37 l/min), the authors simulated three different conditions of respiratory mechanics (normal, restrictive and obstructive) using the three tested ventilators in either a "vented" or "non-vented" configuration. This bench study showed that the behavior of SLC ventilators differs in the volume-guaranteed mode according to the presence of an unintentional leak.

Lellouche and Lipes reported the most recent data which supports the generalization of prophylactic protective ventilation which combines at least lower VT (4–8 ml/kg of predicted body weight) and PEEP in almost all mechanically ventilated patients (both with healthy and unhealthy lungs) [16].

Waisman et al. [17] performed an animal study of progressive pneumothorax induced in rabbits. The authors continuously recorded the hemodynamic parameters, VT, EtCO2, SpO2, blood gases, and chest wall tidal displacements (TDi) on both sides of the chest. The finding

that a counterintuitive transient prolonged the decrease in CO_2 without changes in SpO2 probably explains the delay in diagnosis of pneumothorax encountered in newborn infants [17].

In a review article, Matamis et al. [18] describe the technique and the clinical applications of ultrasonography in the evaluation of diaphragmatic function in ICU patients. Ultrasonography can assess the characteristics of diaphragmatic movement such as amplitude, force, and velocity of contraction, special patterns of motion, and changes in diaphragmatic thickness during inspiration. These parameters provide valuable information to assess weakness or paralysis. Schmidt et al. [19] reported that surface electromyograms (sEMGs) of extradiaphragmatic inspiratory muscles vary with PSV settings and relate to the degree of discomfort and the intensity of dyspnea. A strong correlation was found between dyspnea and EMGmax. Assessing sEMGs could be used as a surrogate of respiratory sensations in mechanically ventilated patients.

Airways

In his "What's New in Intensive Care Medicine", Scales provided an update on recent findings about tracheotomy in critically ill patients [20]. Despite different inclusion criteria and definitions of "early" versus "late" tracheostomy, recently published randomized clinical trials [21–24] indicate that early tracheostomy is not associated with reduced mortality or ICU-acquired infections. Studies in selected patient populations are warranted. In order to assess the safety of percutaneous dilatational tracheostomy (PDT) in critically ill patients receiving extracorporeal lung assist a retrospective observational study was done in 118 patients [25]. Five patients (4.2 %) presented major complications (two procedure-related bleeding, two cases of per procedure pneumothoraxes, and one hypotension with brief and successful cardiopulmonary resuscitation). In addition, minor bleeding complications occurred in 37 patients. Last, Hernandez et al. [26] showed that deflating the tracheal cuff in tracheostomized patients shortens weaning, reduces respiratory infections, and may improve swallowing.

In a before–after study, De Jong et al. [27] evaluated the impact of a new combo videolaryngoscope on the incidence of difficult laryngoscopy/difficult intubation in critically ill patients intubated in the ICU. Among the 210 included patients, 140 were intubated using the standard procedure and 70 using the combo videolaryngoscope, with incidence of difficult laryngoscopy/intubation of 16 and 4 %, respectively ($p = 0.01$).

Touat et al. [28] sought to determine incidence, risk factors, and outcome associated with tracheal ischemic lesions in 96 critically ill patients intubated in the ICU. This was a planned post hoc study from an RCT on the impact of continuous cuff-pressure control on microaspiration of gastric contents [29]. Eighty (83 %) patients had at least one tracheal ischemic lesion, including ischemia (68 %), hyperemia (54 %), ulcer (10 %), and tracheal rupture (1 %). Duration of assist-control mechanical ventilation was the only factor independently associated with severe tracheal ischemia. The majority of severe tracheal ischemic lesions resolved 2 weeks after extubation.

ARDS

Definitions

The definition of ARDS has been recently revisited [30]. An attempt to validate this decision on 278 patients prospectively admitted to ten ICUs failed, with neither the stratification by severity nor the PaO_2/FiO_2 at study entry being independently associated with mortality [31]. The time to assess the criteria is still a matter of debate. In a prospective study [32], it was hypothesized that the value of the PaO_2/FiO_2 calculated under a defined standard ventilatory setting within 24 h of ARDS onset will allow a better phenotypic classification and risk stratification. Patients were studied under four different PEEP and FiO_2 combinations at the onset of ARDS and the same four 24 h later. At ARDS onset, none of the four ventilator settings were capable of separating patients into subgroups with significantly different ICU mortalities. At 24 h after ARDS onset, the only ventilatory setting that significantly correlated the ranges of PaO_2/FiO_2 ratios with ICU mortality was $FiO_2 \geq 0.5$ with PEEP $\geq$ 10 cmH_2O. Using these parameters at 24 h after ARDS onset in the 282 patients from the validation cohort, the authors reclassified 16.7 % of patients as having mild ARDS (ICU mortality 17 %), 52.8 % of patients as having moderate ARDS (ICU mortality 40.9 %), and 30.5 % as having severe ARDS (ICU mortality 58.1 %). This study could be important in designing future trials in order to include patients with established ARDS but is in contradiction with recent studies suggesting that a prompt protective ventilatory strategy (including proning and muscular blockers) is able to improve the outcome. This study along with recent trials strongly supports the idea of including patients with severe ARDS in interventional trials so as to improve survival.

Another important matter of debate in defining ARDS is PEEP setting. There is little information about the right time to assess blood gas after increasing or decreasing PEEP. In order to assess the equilibrium time required for the variables most commonly used in clinical practice, 44 patients were included in a prospective study [33]. In 23 patients (group 1), PEEP changed from 10 to 5 cmH_2O and then from 5 to 15 cmH_2O. In 21 patients (group 2), PEEP increased from 10 to 15 cmH_2O and then from 15

to 5 cmH_2O. Each level of PEEP was maintained for 60 min. Respiratory and hemodynamic parameters were recorded. After the decrease in PEEP, the equilibration time for arterial oxygenation is reached within 5 min. When PEEP was raised, no equilibrium was reached even after 60 min, suggesting that in some patients there is the need to wait more than 1 h to reach the equilibrium period. These findings are important both for clinical practice but also for future investigations using PaO_2 as an endpoint.

Pathophysiology

Regarding pathophysiology, T regulatory cells (Tregs), a subset of CD4 lymphocytes that express CD25 as well as the transcription factor Forkhead box protein 3 on their surface, have been studied in animals. In a clinical study, Tregs were detected in bronchoalveolar lavage (BAL) of controls without lung disease and in ARDS [34]. The mean ratio of Treg cells to all CD4 lymphocytes in patients suffering from ARDS was threefold higher in nonsurvivors (16.5 %; $p = 0.025$) and almost twofold higher in survivors (9 %; $p = 0.015$) in comparison to controls (5.9 %). In contrast, the ratio of Tregs to all CD4 cells in the blood was not associated with 30-day survival. These data highlight the potential impact of Tregs on ARDS and should, therefore, stimulate further research on alveolar cellular mechanisms in human ARDS. SuPAR (soluble urokinase plasminogen activator receptor) and PAI-1 (plasminogen activator inhibitor 1) are active in the coagulation–fibrinolysis pathway. It was hypothesized that elevated serum levels of suPAR and PAI-1 in critically ill patients with ARF are associated with development of ALI/ARDS, sepsis, renal replacement therapy (RRT), and mortality [35]. Serum suPAR and PAI-1 concentrations at baseline and on day 2 were measured in a large prospective Finnish multicenter cohort study. This study showed that patients with the highest quartile of baseline suPAR concentrations had an odds ratio (OR) of 2.52 for 90-day mortality when compared to the lowest quartile. Furthermore, the patients with the highest quartile of baseline suPAR concentration had an OR of 3.16 for developing ALI or ARDS. In post hoc subgroup analyses, these differences were mainly observed in nonoperative patients. In contrast to suPAR concentration, a very weak prognostic value for PAI-1 was observed to predict mortality, sepsis, ALI/ARDS, or RRT.

Exposure to hyperoxia has long been recognized as a potential cause of ALI. Although low doses of oxygen are considered safe, it has been reported that even minimal doses (FiO_2 0.28) increase pulmonary inflammatory mediators in patients with COPD and in healthy volunteers. In the study by Fernandez et al. [36], it was hypothesized that the inflammatory process caused by low-dose oxygen could lead to changes in the redox state at the airway surface that may be characterized by an increase in the concentration of oxidants in exhaled breath condensate (EBC) samples. Thus, the acute effect of reducing FiO_2 from basal 0.40 to 0.21 on pulmonary inflammatory mediators was studied in patients mechanically ventilated longer than 24 h, without severe respiratory failure ($PaO_2/FiO_2 > 250$). Three 4-h periods were tested: (1) FiO_2 0.40, (2) FiO_2 0.21, and (3) FiO_2 0.40. During the last 20 min of each period, EBC was collected for determination of inflammatory mediators (nitrate, nitrite, and 8-isoprostane). Blood samples were also obtained for determination of plasma inflammatory mediators (nitrate, nitrite, TNF-α, IL-4, IL-6, and IL-10). There was no alteration of inflammatory mediators in EBC between the three periods, nor in plasma samples, suggesting that low-dose oxygen does not exert inflammatory effects. However, the sample size limitation does not rule out the possibility that oxygen at this concentration may act differently in different populations.

Lung recruitment

Quantitative lung CT scan analysis remains the reference method for computing PEEP-induced lung recruitment. The accuracy of a visual anatomical lung CT scan analysis was evaluated compared to a quantitative lung CT scan analysis [37]. This analysis does not require any dedicated software or a manual delineation of the lung and is based on the visual assessment of consolidated/collapsed regions on CT lung images. Fifty sets of two complete lung CT scans of ALI/ARDS patients were analyzed. The first lung CT scan was performed at an inspiratory plateau pressure of 45 cmH_2O during an end-inspiratory pause and the second one at a PEEP value of 5 cmH_2O during an end-expiratory pause. A visual four-step scale (0–25, 25–50, 50–75, and 75–100 %) was used to quantify the percentage of the collapsed/consolidated tissue in each segment of the lung. The time required for the visual anatomical and for the quantitative lung CT analysis ranged between 20–30 min and 5–6 h. The receiver operating characteristic (ROC) curve showed that the optimal cutoff value for the visual anatomical analysis for predicting patients with high lung recruitability was 8.9 % (area under the ROC curve = 0.92). Considering this cutoff, there were 24 true positives, six false positives, 19 true negatives, and one false negative; thus the sensitivity, specificity, and diagnostic accuracy were 0.96, 0.76, and 0.86 respectively. There are some limitations of visual anatomical analysis. In the present study there was a moderate interobserver variability of the operators in assessing the extension of the consolidated area in the bronchopulmonary segments as attested by a kappa coefficient of 0.62. Moreover this evaluation was done by two radiologists and it is difficult to extrapolate the results to ICU physicians. For example, it can be a difficult to identify the single segments of each lobe by recognizing

the anatomic boundaries. Finally this new technique does not allow the evaluation of overinflation.

Spontaneous ventilation is characterized by considerable respiratory rate variability (RRV). Gutierrez et al. [38] enrolled 178 patients, of whom 47 had high RRV and 131 low RRV. Airway signals and modes of ventilation were continuously recorded for over 80 % of the time patients were receiving ventilatory support. Patients exhibiting a low RRV during most of their time under ventilatory support were at greater risk of dying than those with high RRV. This study supports the idea of respecting high respiratory rate when spontaneous ventilation is allowed but needs further confirmation.

In a study including 24 invasively ventilated patients with or without tracheostomy and experiencing weaning difficulties, three positions were consecutively applied during 15 min: the supine position, the 45° semi-seated position, and the nearly seated position (simulating the 90°LD position) [39]. Concerning the patients' opinion, the 45° position was associated 12 times with the best score, the 0° position 7 times, and the 90°LD 6 times. PEEPi was slightly and significantly higher in supine compared with the 45° and the 90°LD positions. All parameters of respiratory effort were significantly lower in the semi-seated position, as compared with the other two positions. The seated position was significantly associated with the highest effort-to-breathe and P0.1 values ($p = 0.01$). This study suggested that in difficult-to-wean patients, the best position is the semi-seated position and not the seated position.

In their "My paper 20 years later", Gattinoni et al. [40] reported on their "sponge model" published in 1991 where they described that shifting an ARDS patient from supine to prone position led immediately to the inversion of the inflation gradient and to a redistribution of densities from dorsal to ventral lung regions, with improved oxygenation.

ECMO

In the last few years, extracorporeal, pumpless arteriovenous approaches to CO_2 removal using an artificial membrane lung have been developed and tested for clinical use demonstrating increased CO_2 removal and moderate oxygenation improvement associated with the possibility of reducing VT. Bein et al. [41] did the first multicenter RCT investigating the effects of combining a VT of 3 ml/kg predicted body weight with arteriovenous extracorporeal CO_2 elimination (avECCO2-R) in patients with an established ARDS (PaO_2/FiO_2 <200 after 24 h despite optimal supportive treatment). The primary outcome parameter was the number of ventilator-free days (VFD) both at 28 and 60 days. During a 3-year period, 79 patients were included. There was no statistical difference regarding the number of VFD. However, a post hoc analysis demonstrated that patients with a PaO_2/FiO_2 <150 at randomization treated with avECCO2-R had a significantly increased VFD at day 60 (40.9 ± 12.8) compared to controls (28.2 ± 16.4, $p = 0.033$). This study suggests that severe ARDS patients are the best targeted population to evaluate the impact of a strategy on the ARDS outcome.

After the first phase of extracorporeal membrane oxygenation (ECMO) with patients remaining sedated and paralyzed, spontaneous ventilation is allowed prior to ECMO weaning. During this difficult period of time, PSV may be difficult to implement in these patients with a reduced compliance, likely because peak inspiratory flow is reached rapidly and the flow-based expiratory phase of PSV starts while the patient is still inspiring (premature expiratory cycling). These patients are therefore at high risk of patient–ventilator asynchrony. Diaphragm electrical activity (EAdi) represents a clinically reliable monitor of the respiratory center's neural activity and in the assessment of patient–ventilator asynchrony. In a study by Mauri et al. [42], EAdi-based analysis of asynchrony showed that ineffective triggering was the least represented pattern during PSV, whereas premature cycling was the most frequent. During NAVA, the incidence of premature cycling decreased, and all patterns became more equally represented. This study suggests the idea that when spontaneous ventilation is allowed in ARDS patients under ECMO, the respiratory drive remains important and if using PSV, expiratory cycling time should be reduced. Further studies are needed in order to assess the potential beneficial effects of NAVA in reducing the duration of mechanical ventilation and ECMO in severe ARDS patients receiving ECMO.

Some recent reports suggested that, in specialized centers, ECMO could be useful in improving the outcome of the most severe ARDS patients. ECMO settings are important to understand in order to improve blood oxygenation and/or decarboxylation. In the study by Schmidt et al. [43] determinants of blood oxygenation and decarboxylation were assessed in a series of 10 patients receiving venovenous ECMO. Arterial oxygenation was mainly related to the ECMO blood flow and to the fraction of inspired oxygen in circuit. In contrast decarboxylation was mainly related to the sweep gas flow through the oxygenator. An ECMO flow/cardiac output >60 % was constantly associated with adequate blood oxygenation. As we are in our learning curve in identifying who could benefit from ECMO, predictors of success are important to investigate. Several recent scores for predicting the outcome of ARDS patients under ECMO have been published in *Intensive Care Medicine* [44–46]. The PRESERVE score is based on eight pre-ECMO variables (age, body mass index, immunocompromised status, prone position, days of mechanical ventilation, SOFA, plateau pressure and PEEP [44]. The ECMOnet score [46] is based on the duration of hospital stay prior to ECMO, the bilirubin and the creatinine levels,

the hematocrit, and the mean arterial pressure, all collected prior to ECMO. In Roch's study of 85 patients equipped with ECMO by a medical mobile team, the score included age, SOFA, and a diagnosis of influenza [45]. All these scores need to be used and may be compared in future trials.

Distelmaier et al. [47] prospectively evaluated the impact of COPD on cardiovascular and all-cause mortality in 191 patients who underwent venoarterial ECMO support following cardiovascular surgery. Patients were followed up for a median of 51 months (IQR 34–71 months) and the overall mortality was 65 %. Deaths were due to cardiovascular causes in 88 %. Survival was substantially lower in COPD patients, compared to non-COPD patients, at 1 year (23 vs. 44 %) and after 6 years (14 vs. 35 %). In addition, the authors demonstrated that COPD was independently associated with both all-cause [hazard ratio (HR) = 4.22 (95 % CI 1.04–17.11, $p = 0.04$)] and cardiovascular [HR = 5.87 (95 % CI 1.41–24.47, $p = 0.02$)] mortality. As information on long-term outcomes in patients who were supported with ECMO is scarce, the results of this study can assist physicians, patients, and families in decision-making. In addition, COPD patients might represent a subgroup of patients that can benefit from intensified treatment of co-morbidities and close checkups after hospital discharge. Likewise, Al-Soufi et al. [48] reported that high body weight should therefore not be regarded as a contraindication to initiation of venovenous ECMO in adult patients. Last, Ferrie et al. [49] reported that enteral feeding can be well tolerated by patients who are receiving venovenous or venoarterial ECMO.

All these advances in various aspects of oxygenation in patients with ARDS have been thoroughly addressed in the "what's new" paper from Papazian and Herridge [50]. Other aspects related to the use of venovenous ECMO in ARDS patients were addressed in another what's new paper from Abrams et al. [51].

Quality of life

There is a paucity of published work on longer-term outcomes after septic shock. In a single-center study, Nesseler et al. [52] evaluated survival and health-related quality of life (HRQoL) 6 months after ICU admission. Ninety-six patients were studied and 6-month mortality was high at 45 %. In multivariable regression modeling, survivors were found to be younger, have lower lactate levels on admission and lower SAPS II scores, less RRT, less corticosteroid administration, and longer hospital length of stay. Most survivors were able to return home. SF-36 was evaluated 4 weeks prior to ICU admission and at 6 months following critical illness. An important limitation included proxy ascertainment of baseline HRQoL. All domains of the generic HRQoL measure (SF-36) were below those predicted for the general population both before and after ICU admission. The authors noted an important increase in the Physical Component Score (PCS) at 6-month follow-up, but this still remained below that reported for the general population. In the paper by Schmidt et al. [44] mentioned above, investigators also evaluated longer-term HRQoL and psychological outcomes in 140 ARDS patients receiving ECMO between 2008 and 2012. There has been a very pervasive pessimism and scarcity of data on long-term outcomes after critical illness complicating hematological or solid malignancy. In a prospective, single-center observational study of 483 patients, Oeyen et al. [53] assessed HRQoL outcomes at 3 months and 1 year after ICU discharge and compared these outcomes to HRQoL before ICU admission. Median age was 62 years and the majority were men with a solid malignancy. More patients died in the hematologic malignancy group compared to the solid malignancy group at 3 months and again at 1 year. HRQoL was low at 3 months and although improved by 1 year, still remained below the age- and sex-matched control population. Older age, important burden of comorbid disease, and hematologic malignancy were each associated with poor HRQoL at 1 year. These authors advocate the inclusion of this longer-term outcome information as part of the discussion and decision-making prior to referral for ICU admission. HRQoL and psychological outcomes after NIV for those who have declined invasive endotracheal intubation are not well characterized. Azoulay et al. [54] performed a prospective longitudinal multicenter study (54 centers in France and Belgium from 2010 to 2011) of all patients on NIV and compared outcomes for those with no treatment-limitation decisions to those who declined intubation. Survivors and their relatives on day 90 post ICU discharge were interviewed by phone to ascertain their HRQoL, and symptoms of post-traumatic stress disorder (PTSD), anxiety, and depression. Hospital mortality was greatest for those who declined intubation and the COPD subgroup had the highest survival. Further, patients in this group showed no reduction from baseline in 90-day HRQoL and the prevalence of symptoms of PTSD, depression, and anxiety was similar to that reported by patients who had no limitation in treatment and their relatives. In this important study, NIV helped to prolong life in a significant proportion of survivors who had preserved HRQOL at 90-day follow-up and without any additional decrement in psychological health compared to patients with no treatment-limitation decision. NIV may represent a very viable treatment option in those who decline IMV.

"Ethics and legal" section

In the past year, *Intensive Care Medicine* has published a number of important articles in the "ethics and legal" section that have addressed a diverse group of topics including the long-term effect of intensive care on patients and their families, the perspectives of patients

and of clinicians on end-of-life care in the ICU, the factors that contribute to physician and institutional variability in end-of-life care in the ICU, the incidence of potential missed organ donors in the ICU and emergency department, and the ethics and practice of research in the ICU setting.

Long-term effect of intensive care on patients and their families

An important yet understudied area of intensive care is the influence of the ICU environment on patient and family outcomes. Jongerden et al. [55] performed a study examining patient and family satisfaction with care before and after the ICU was moved from a multiple bed-per-room older ICU to a new ICU with single rooms. They used standardized and validated surveys of patient and family satisfaction and had an overall response rate from a patient or family member for each patient of 63 %. They found that both patient and family satisfaction increased after the move to the new ICU, demonstrating the importance of the ICU environment to patient and family satisfaction. As satisfaction with care is increasingly considered a marker of quality of care, it is important to consider the diverse factors that influence patient and family satisfaction. Another study exploring family satisfaction in the ICU was an observational study performed in four ICUs of a single university hospital in Germany by Schwarzkopf and colleagues [56]. This study was a combination of quantitative and qualitative methods to explore the determinants of family satisfaction. They enrolled 215 family members representing a response rate of 28 % and found overall fairly high satisfaction (78.3 on a scale from 0 to 100) with no patient or family factors associated with higher satisfaction. The themes that were most associated with higher satisfaction included decreased patient agitation; increased consistency, clarity, and completeness of information; emotional support; and respect and compassion shown toward the family. Interesting, the physical features of the ICU waiting room and the ICU atmosphere were also important determinants of family satisfaction. These studies used mixed methods (quantitative and qualitative) to provide a better understanding of the components if ICU care that family members view as important. Finally, Jones contributed a "What's New in Intensive Care Medicine" article entitled "What's new on the post-ICU burden for patients and relatives?" [57]. This article reviews the diverse long-term burdens of critical illness including cognitive, physical, and psychological sequelae. The article also describes the evidence suggesting the potential benefit of rehabilitation after critical illness, but reviewing the mixed results of studies attempting to use rehabilitation. Dr. Jones provides a conceptual model for the trajectories of care after critical illness that could be used to guide rehabilitation efforts in the future. Last, Giannini et al. [58] assessed the impact of partial liberalization of ICU visiting policies associated with staff burnout. If doctors and nurses overall viewed the policy positively, having negative views on open visitation policies strongly correlated with burnout.

Perspectives of patients and clinicians on end-of-life care in the ICU

Intensive Care Medicine published an interesting two-part study exploring intensive care for elderly patients. Given our aging population, this is an important topic for guiding use of intensive care resources in the future. In the first part of this study, Philippart and colleagues performed an observational study of consecutive community-dwelling elderly individuals previously hospitalized in acute care as well as volunteers residing in nursing homes or assisted-living situations in France [59]. Participants viewed films of different ICU therapies including NIV, IMV, and RRT in conjunction with IMV (RRT-IMV). They had 115 participants with an 87 % participation rate. They found that refusal rates for these therapies were 27 % for NIV, 43 % for IMV, and 63 % for RRT-IMV. Demographic factors associated with higher refusal rates of some treatment included being married and female sex; however, lower quality of life was associated with higher refusal rates of all treatments. In the second part of this study, Garrouste-Orgeas and colleagues reported the results of a simulation study examining physician decisions regarding the care of patients aged over 80 [60]. The simulation involved decisions about NIV, IMV, and RRT-IMV and included variation in bed availability and patient preferences. The investigators enrolled 100 physicians (46 % participation rate) and found a high degree of variability among physicians in decisions about provision of intensive care for the simulated elderly patient. Factors associated with increased utilization of ICU therapies, not surprisingly, included younger patient age, higher patient functional status, increased bed availability, and patient preference for life-sustaining treatment. Perhaps one of the most interesting findings from this study was the high degree of variability among physicians in decision-making for elderly critically ill patients. The high degree of influence of patient preferences, in combination with the prior study from this group showing patients had diverse preferences, reinforces the importance of advance care planning among elderly patients. Finally, a study of visiting policies in a pediatric ICU provides insights into care at the opposite end of the age spectrum. Giannini conducted a before–after study in eight Italian ICUs who were changing their family visiting policies to increase family visiting hours to at least 8 h per day [58]. They surveyed ICU nurses and physicians before, 6 months after, and 12 months after the liberalization of visiting hours and assessed attitudes toward the new policy as well as

clinician burnout. Their response rates at each time point exceeded 70 % and they found an increase in burnout from 35 % before to 43 % 12 months after the policy change. Importantly, they also found extremely positive perspectives on the liberalization of visiting hour policy at all time points. This important study suggests that most ICU nurses and physicians understand the importance of liberalizing visiting hours in pediatric ICUs, but may need support to accommodate the increased job stress that open visiting hours places on nurses and physicians.

Factors that contribute to physician and institutional variability in end-of-life care in the ICU

Studies suggest a significant variability in intensity of care at the end of life and this intensity seems to vary by region, institution, and physician. Wilson and colleagues conducted a single-center qualitative study to explore the reasons for physician variability in decisions to limit life support in the ICU [61]. They interviewed 17 intensivists and 10 ICU nurses from both medical and surgical ICUs. They identified four themes that influenced physician variability in decisions including the physician work environment inclusive of workload and incorporation of nursing input, physicians' prior experience with unexpected survival and limiting life support, physician attitudes and values, and physicians' relationships with patients and their family members. Identification of these factors may help guide interventions to minimize unwarranted variation in physician decision-making. A remarkable study exploring the determinants of institutional variation in intensity of care at the end of life was conducted by Barnato et al. [62]. These investigators conducted a mixed methods case study at two academic medical centers that were at opposite ends of the spectrum for intensity of end-of-life care in the ICU as a way to understand the cultural differences between the institutions. The investigators observed rounds, conducted semi-structured interviews with staff, patients, and families, and collected artifacts including standardized forms and protocols. They found important differences in the cultures of the two institutions with the low-intensity institution more likely to use time-limited trials of intensive care, to make an earlier diagnosis of "dying", and to have physicians with a higher self-efficacy for making decisions about limiting life-sustaining treatments. This study provides important insights into some of the underlying "institutional culture" differences that may lead to unwarranted variation in decision-making about end-of-life care in the ICU.

Incidence of potential missed organ donors in the ICU and emergency department

There is a worldwide shortage of organ donors that limits the life-prolonging potential of organ transplantation. Kutsogiannis and colleagues conducted a retrospective study of all deaths in ICUs and emergency departments that were not referred for evaluation for organ donation in four hospitals that cover a large geographic region in Canada over a 2-year period [63]. Of 2,931 deaths, 64 patients were identified as having a high probability of progression to brain death and 130 patients were assessed for possible donation after circulatory death. On the basis of calculations for the region, they found that the number of brain death or donation after cardiac death (DCD) organ donors represented by missed referrals may represent up to 7.5 donors per million population. This study identifies the importance of improving documentation of brainstem reflexes and encouraging referral of patients suffering cardiac arrest to organ procurement specialists. Recent advances in the field of organ donation have been thoroughly addressed in the "what's new" paper from Al-Khafaji et al. [64].

Ethics and practice of research in the ICU setting

There has been increasing research in the last few years into the ethics and practice of clinical research in the ICU setting. Given the challenges and importance of research in the critical care setting, this is a key area of focus. In this context, Gigon and colleagues investigated the impact of a study's invasiveness on the choice of who should provide consent and the approach to informed consent [65]. At ICU discharge, patients and family members were randomized to receive a vignette of a noninvasive or an invasive study and each vignette included questions about both a conscious and an unconscious patient. They enrolled 185 patients, and 125 family members, with response rates of 40 and 65 %, respectively. The invasiveness of the study had no impact on respondents' choices for who should give consent, but the more invasive study prompted respondents to be more likely to request more than one person to provide consent and decreased acceptance of deferred or two-step consent. In another observational study conducted in a single center in Australia, Potter and colleagues examined patients enrolled in the NICE-SUGAR study in which delayed consent was used [66]. They enrolled 298 NICE-SUGAR participants (79 % response rate) for which delayed consent was obtained for 27 % of participants and surrogate consent for 72 %. Of these participants, 96 % would have participated in NICE-SUGAR if asked prior to enrollment and 82 % would have ranked the person who actually consented on their behalf as their first choice. These authors concluded that the consent approach used in NICE-SUGAR, including delayed consent when a surrogate was not available, was acceptable to the vast majority of study participants. Finally, in a "What's New in Intensive Care", Kompanje reviewed the proposed revisions for human subject research in the

Declaration of Helsinki [67]. The proposed revisions have stronger and more direct wording about the protections necessary for vulnerable patients, which are important in many settings. However, these revisions could be interpreted in a way that makes clinical research in the emergency and intensive care setting more difficult, potentially resulting in delays in enrolling patients and increased refusal rates. The intensive care community must be centrally involved in these decisions to allow us to provide protection for our vulnerable population of critically ill patients and their families while at the same time ensuring we are able to conduct timely and efficient research that is valid and generalizable in order to improve outcomes for all critically patients and their families. Interestingly, Cook et al. [68] stressed how tracking, analyzing, interpreting, and reporting the rates and reasons for physicians declining to allow their patients to be approached for enrollment provides insights into clinicians' concerns and attitudes to trials. Last, Sprung and the Eldicus investigators, consultants, and experts provided an updated consensus statement on the triage of patients for ICU beds. They reached a consensus for most general and specific ICU triage principles and recommendations [69].

Safety

Although attention to patient safety has considerably increased over recent years, progress has been frustratingly slow. One of the reasons is probably that health professionals and managers focused too much on procedures and care bundles than on improvements at the bedside. As clearly stated by Garrouste-Orgeas and Valentin in a "What's New in Intensive Care Medicine" on patient safety [70] a major change is necessary to replace the culture of blame and shame by a culture of learning in which risk management is an integral part of the thinking of health-care providers. This year, several articles published in the journal focused on the potential beneficial impact of such cultural evolution on the quality of care and on how one can foster such an evolution in the ICU.

Valentin et al. [71] used the Vienna safety climate questionnaire to assess medication and dislodgement errors in routine intensive care practice. They recruited 795 patients in 57 ICUs, and a total of 641 errors affecting 269 patients were reported (rate of 49.8 errors per 100 patient days). The authors found that a better safety climate was associated with 0.67 lower odds of at least one medical error after adjustment for the workload in the unit and the number of tubes/lines/catheters/drains at the patient level. Physical restraint is used in many ICUs worldwide to reduce the loss of artificial airways and unplanned dislodgment of lines, catheters, and drains. However, De Jonghe et al. [72] found that physical restraint was used in more than 50 % of awake, calm, and co-operative patients in 29 % of the 130 participating ICUs. Only 21 % of the ICUs had a written local procedure concerning the use of physical restraint. Along this line, Pelieu et al. [73] assessed whether organizational culture was associated with the handling of medical errors. Organizational culture was assessed by the organizational culture inventory, a 120-item scale with 12 dimensions. The authors found that task-security-oriented culture was significantly associated with a preventable judgment, whereas people-security-oriented culture was significantly associated with an unpreventable judgment. Another important finding of this study is that after implementation of morbidity and mortality conferences a change in organizational culture occurred over time: team-satisfaction-oriented culture took a leading role, whereas people-security oriented culture dramatically decreased. Ten Have et al. [74] performed a nonrandomized study to assess whether leadership training could improve the quality of interdisciplinary rounds in four ICUs for adults in the Netherlands. The intervention consisted of a 1-day training session in a simulation environment and feedback sessions of videotaped behavior in the workplace. There was an improvement in seven of the ten essential quality indicators of the interdisciplinary rounds assessment scale from before to after training, and even more impressive is that the intervention groups after training had better performance than the control group in eight indicators despite being less experienced. Finally, in his "What's New in Intensive Care Medicine", Kahn [75] provided an update of the potential mechanisms of volume–outcome relationships.

Methodological issues

Two articles addressed the quality of statistical reporting in critical care journals. Latronico et al. [76] evaluated the methodological quality of RCTs published in *Intensive Care Medicine* from 2001 to 2010 and compared it to a previous review of RCTs from 1975 to 2000. They found that the quality of reporting of RCTs published partly improved over time and that spin and delta bias were often present. Spin bias refer to reporting strategies to distract the reader from statistically non-significant results, whereas delta bias refer to the inflation between predicted and observed treatment effect. Stronger adherence to the Consolidated Standard of Reporting Trials (CONSORT) recommendations, with special emphasis on accurate description of randomization and blindness, and correct reporting of statistically non-significant results are warranted. Another article by Vesin et al. [77] assessed the quality of reporting and handling missing values in

clinical studies. They concluded that missing data was common in the ICU literature and that it can generate interpretation biases. They also provided guidance on the management of clinical study analysis in case of missing data.

Awissi et al. [78] performed a systematic review of the literature to assess the prevalence, risk factors, screening tools, prophylactic and treatment strategies, and outcome of alcohol withdrawal syndrome and delirium tremens in the critically ill. They found that reported alcohol withdrawal syndrome rates range from less than 1 % in general ICU patients to 60 % in highly selected alcohol-dependent ICU patients. Treatment of alcohol withdrawal syndrome was associated with higher ICU complication rates and resource utilizations. Drolz et al. [79] assessed the clinical impact of arterial ammonia levels in ICU patients with different liver diseases. They found that peak ammonia concentrations were independently associated with 28-day mortality or liver transplantation in hypoxic hepatitis and alcoholic liver failure, respectively. There was, however, no association between mortality and arterial ammonia in patients with liver cirrhosis and in patients without evidence of liver disease.

Hematological issues in the critically ill

Thrombocytopenia is a frequent finding in the critically ill. Platelets play an essential role in the complex interaction between inflammation and coagulation. Three studies provided new insights on this topic with potential implications for patient management. In a very interesting prospective multicenter study, Thiolliere et al. [80] evaluated 301 patients with either absolute (platelet count $<100 \times 10^9$/l) or relative (decrease in the platelet count >30 %) thrombocytopenia. The frequencies of absolute and relative thrombocytopenia were 8.9 and 6.7 %, respectively. Multiple reasons for thrombocytopenia were diagnosed in three quarters of the patients, with sepsis and disseminated intravascular coagulation the most frequently identified. Moreover, serious bleeding events were an independent risk for death and platelets count less than 50×10^9/l predicted the occurrence of such adverse events. This study is also unique as the authors performed an extensive diagnostic workup including the examination of bone marrow aspirations in the vast majority of patients. They demonstrated that bone marrow aspiration yielded novel diagnoses in 22 % of patients, resulting in significant impact on management in 11 % of patients, particularly in those with absolute thrombocytopenia. De Blasi et al. [81] investigated whether changes in the percentage of immature platelet fraction (IPF %) could be useful in predicting the development of sepsis over the first week of ICU stay in critically ill patients without sepsis at ICU admission. They demonstrated that significant increases in IPF values preceded the subsequent development of sepsis by a median of 2 days. IPF values greater than 4.7 % yielded a sensitivity of 56.2 % (95 % CI 37.7–73.6 %) and a specificity of 90 % (CI 73.4–97.8 %). In addition, IPF % was inversely correlated with platelet count in patients who developed sepsis. Last, Mariotte et al. [82] evaluated 86 patients with thrombotic thrombocytopenic purpura (TTP) admitted to a referral ICU. They used a pragmatic operational definition to classify 37 (43 %) patients with unresponsive TTP (Un-TTP). They identified four easily available factors independently associated with unresponsiveness: age older than 60 years, cardiac and neurological involvement by TTP, and platelet count lower than 15×10^3/l on day 2. According to the authors, these predictors can assist in the identification of patients with TTP who might benefit from early treatment intensification.

In their "What's New in Intensive Care Medicine" on transfusion, Hajjar and Vincent [83] reviewed the recently published studies reporting results that raise concerns on the use restrictive transfusion strategy in some subgroups of patients requiring intensive care. This issue becomes even more critical as blood collection, processing, and storage have improved, which may prevent and minimize many of the known adverse effects of blood transfusion. Considering such findings and the heterogeneity of clinical scenarios involved in critically ill patients, the authors claim for the need to rethink our transfusion practice in sicker patients and, in parallel, encourage intensivists to balance the risks of anemia and transfusion at the bedside, instead of making decisions using simple transfusion thresholds.

Critically ill patients frequently present with multiple risk factors for venous thromboembolism (VTE). Moreover, many patients have high risk of bleeding, thus limiting the use of anticoagulant prophylaxis. In these patients, current guidelines advocate the use of mechanical thromboprophylaxis with graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC) at least until the bleeding risk decreases [84]. However, the efficacy of mechanical VTE prevention in critically ill patients has not been evaluated yet. To address this question, Vignon et al. [85] conducted a multicenter, open-label RCT including 407 patients with a high risk of bleeding randomly assigned to receive IPC associated with GCS or GCS alone for 6 days during their ICU stay. The occurrence of a VTE between days 1 and 6 was considered the primary endpoint. VTE occurred in 5.6 % (10 of 179 patients) in the IPC/GCS group and 9.2 % (17 of 184 patients) in the control group (relative risk 0.60; 95 % CI 0.28–1.28; $p = 0.19$). Morality rates were comparable between the groups. In addition, compliance and tolerance of IPC were relatively good. However, as pointed by the authors, the trial was not able to demonstrate the superiority of the combination of IPC/

GCS compared to GCS alone in preventing VTE in ICU patients at high risk of bleeding because of the lack of statistical power.

Recombinant human erythropoietin (rhEPO) has been demonstrated to protect against kidney ischemia/reperfusion (I/R) injury in experimental studies. However, clinical studies yielded controversial results. Matějková et al. [86] investigated whether the infusion of carbamylated erythropoietin-FC fusion protein (cEPO-FC) or rhEPO would protect against kidney I/R injury in pigs with atherosclerosis submitted to aortic occlusion. They observed no differences in markers of renal function, systemic inflammation and oxidative and nitrosative stress, as well as in histopatological apoptosis or glomerular and tubular damage among animals receiving cEPO-FC, rhEPO, or vehicle. In a systematic review and meta-analysis involving 944,856 participants (48 studies), Mesgarpour et al. [87] reported that administration of erythropoiesis-stimulating agents was associated with a significant increase in thrombotic events but not with other frequently reported adverse events and death.

Conflicts of interest None.

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