Consider delayed immunosuppression into the concept of sepsis

To the Editor: In a position statement, Carlet et al. (1) elegantly discuss the difficulty in using the current concept of sepsis for future clinical trials and propose two new strategies. They conclude that a systematic assessment of potential target mediators should be performed and that the underlying rationale and available data for the intervention should be robust and plausible. The second suggested approach focuses on specific disease-oriented studies.

We agree that a dramatic change in study design will be necessary and that the concept of sepsis needs to be reconsidered. Mixing up of patients with various infections in different disease states and immunologic phases in a single clinical trial seems outdated. In addition to the proposed approaches, we suggest a complementary strategy for future clinical trials. This strategy was postulated by us and others a number of years ago (2) and is based on the observation that the vast majority of nonsurviving septic shock patients do not die of the initial burden, but rather from a “second” or “third hit” in later stages of the disease (3). This is due to the fact that most nonsurvivors develop a state of functional immunodeficiency that includes, among others, disturbed monocytic phagocytosis, cytokine profiles, and antigen presentation, as well as dysfunction and apoptosis of lymphocytes, and finally a “shutdown” of innate and adaptive immunity. This state was termed immunoparalysis and may best be approached via standardized quantitative measurement of a diminished monocytic human leukocyte antigen (HLA)-DR expression. Interestingly, although intensivists routinely monitor a wide array of acute organ dysfunctions, the host’s immune system/organ is typically not within the scope and most patients are still characterized using conventional biomarkers such as e.g., high-sensitivity C-reactive protein or procalcitonin. These biomarkers, however, do not reflect the respective phase of the host’s response and are inadequate for an assessment of the immunologic dynamics and of cell-mediated immunity (4). In addition to monitoring the clinical course and established biomarkers, we suggest a longitudinal assessment of cell-mediated immunity via standardized HLA-DR measurement (coefficient of variation: intra-lab 3%, inter-lab 18%). Although more knowledge on the immunopathophysiology of sepsis and more biomarkers for the characterization of cellular immunity is needed, such efforts seem to be a prerequisite for risk stratification, longitudinal follow up, and the design and testing of specific immunologic interventions. Today, the course of monocytic HLA-DR may best reflect the impact of a given immunologic intervention. It can serve as a guide for determining which intervention should be applied at what time to which individual and may assist in both homogenizing study populations and improving the outcome from severe infection.

Our proposed strategy thus aims not only to characterize respective patients, but also strives to therapeutically influence the dysregulation which is—at least partially—responsible for the high mortality observed in sepsis (4). Large-scale clinical trials on immunomodulatory therapies that have been demonstrated to reverse this condition may then be performed. Respective approaches include measures of both immunostimulation (e.g., interferon-γ or granulocyte-macrophage colony-stimulating factor [5]) and on selective removal of inhibitory factors (6). We hypothesize that we will not profoundly influence long-term survival from sepsis until we start to focus on the delayed immunosuppression and the host response.

The authors have not disclosed any potential conflicts of interest.

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The randomized controlled trial needs critical care

To the Editor:
The study by Ospina-Tascon et al. (1) selected the best therapeutic trials in critical care. They found 72 multicentered randomized controlled trials (RCTs) with at least 50 patients using mortality as an end point. They conclude that we should reconsider the problems and possibilities of mortality as an end point. However, it is doubtful whether just a change of end point will be sufficient. The study results can be analyzed in a meta-analysis where we consider all of the different interventions as the intervention and consider an RCT as the level of interest. We can then calculate the absolute difference in mortality, the number of lives saved or lost per trial, based on the number of patients in each trial. The sum is 285 lives saved in 53,705 patients from 72 trials. This is not significantly different from zero (p = 0.348, one sample Student’s t test). The mean absolute number of lives saved per trial is 4 (SD 35, 95% confidence interval [CI] –4 to +12) and has a normal distribution (one sample K-S test, p = 0.11). The mean crude mortality in the control arm is 37.4% (SD 16) and in the interven-
tion arm is 37.3% (SD 14). These are not significantly different (mean difference -0.14, SD 10.6, 95% CI -1.98 to +2.26, p = 0.89 paired samples Student’s t-test).

In other words, the results found in the trials could have been determined purely by chance. Our statistical approach here may be somewhat superficial, but the results are robust enough to raise concern.

The authors suggest that end points other than mortality may be needed, but do not suggest what end points these may be. There may be a natural tendency to choose end points, which are forerunners of mortality, but they are not likely to be promising if we have been unable to show reduced mortality in more than 53,000 patients. However, a different interpretation of the results suggests that 1) our methods of selecting potentially beneficial interventions has been lacking or 2) the way in which we test interventions in RCTs needs improvement. These avenues should also be considered as well as the author’s advice regarding end points other than mortality. The existence of RCTs in the literature indicates that there is considerable interest and energy in the scientific community toward solving these problems. If we apply these resources to improve all aspects of RCTs, not just the end points we choose, we should find a way in improving the care for critically ill patients.

The authors have not disclosed any potential conflicts of interest.

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The challenge of clinical trials in the intensive care unit

To the Editor:

We thank van Meurs et al. (1) for their interest in our review on multicenter randomized controlled trials evaluating mortality as the primary outcome in intensive care unit patients (2). In view of the considerable variability in the interventions studied in the different randomized controlled trials, we are not convinced that a meta-analysis can be performed, and if conducted are uncertain of its utility. Additionally, if performed, calculation of odds ratios with confidence intervals would be better than a Student’s t-test.

We maintain that well-conducted trials focusing on morbidity or on a combination of mortality and morbidity could provide important information. Nevertheless, the most important limitation to all randomized controlled trials in critically ill patients is the heterogeneity of the patient populations studied. Studies randomizing “critically ill”, “septic”, or “acute respiratory distress syndrome” patients to management by higher or lower transfusion thresholds, higher or lower oxygen delivery (DO2), higher or lower positive end-expiratory pressure levels are too likely to be negative, simply because although some patients may indeed benefit from the intervention, in others it will be harmful, so that the net result is negative. Thus, we agree with van Meurs et al. that improving randomized controlled trials is not only a matter of selecting different end points, but also, and perhaps primarily, a matter of improving patient selection.

The authors have not disclosed any potential conflicts of interest.

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Alkalemia during continuous renal replacement therapy

To the Editor:

By using a large retrospective cohort of patients, Demirjian et al. (1) observed that metabolic alkalosis induced by continuous renal replacement therapies (CRRT) is not associated with an increased mortality. The authors anticipated this deleterious effect on the basis of studies having observed some modifications of ionized calcium concentration or left ventricle contractility during alkalosis induced either by hemodialysis or by sodium bicarbonate administration (2, 3). In their study, ventilatory depression is likely to have been overwhelmed by mechanical ventilation. Therefore, it would be interesting to know if the results were identical in mechanically or spontaneously ventilating patients (if any)? It is important to figure out if the patients were able to regulate CO2 elimination or if the intensivists did reduce the observed alkalosis by modifying the ventilatory settings.

One way to consider these results, if the mortality risk is actually not increased by the CRRT-induced metabolic alkalosis, would be to investigate further the other potential deleterious effects of this mild acid–base disorder. One other way would be to avoid it. Effectively, once again this study raises the question of the ability of usual substitution fluids to maintain acid–base equilibrium following the first days of hemofiltration. To address this question, it would have been useful to report the overall ion balance induced by the association of ultrafiltration with substitution fluid administration and optional additional dialysis. Furthermore, the knowledge of the evolution over time of the strong ion difference would be essential to figure out what were the main causes of the observed metabolic alkalosis.

We currently know that metabolic alkalosis is not, as believed in the past, the consequence of pure molecular bicarbonate administration but is rather the effect of several other mechanisms, some of them being exerted by CRRT. According to evidence-based conceptions of the acid–base equilibrium, the main causes of metabolic alkalosis which are related to hemofiltration may either be increased strong ion difference, free water removal, or phosphate normalization (4). Some recent observational data suggest that CRRT induces metabolic alkalosis by removal of unmeasured anions, increasing phosphate, and reducing chloride concentrations in association with the persistence of hypoalbuminemia (5).

By confirming the existence of a metabolic alkalosis imputable to CRRT, because of the accumulation of unmeasured anions this study supports the hypothesis that renal metabolic acidosis is often
“treated” by developing a metabolic alkalosis by some other means than catabolites and toxins removal. This emphasizes the importance of the measurement of the extracorporeal clearance (or dialysis dose) rather than by just considering pH or alkalemia.

Furthermore, to avoid alkalosis, the composition of substitution fluids used for CRRT may require to be slightly modified especially when used for high clearance hemofiltration. The potential alterations having to be investigated could be a slight increase of chloride concentrations and/or the reintroduction of low concentrations of lactate in association with a slightly reduced bicarbonate concentration.

The author has not disclosed any potential conflicts of interest.

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The authors reply:

To the Editor:

We welcome Dr. Journois’s thoughtful comments. With regards to respiratory status, the results were adjusted to baseline ventilation status at initiation of continuous renal replacement therapy.

We calculated the strong ion difference and strong ion gap in the setting of alkalosis (pH > 7.45) while on continuous renal replacement therapy in approximately 70% of time points (excluding lactate). Regardless of day of continuous renal replacement therapy, alkalosis was associated with slightly elevated strong ion difference, and positive strong ion gap; whereas serum chloride was within normal range (Fig. 1). In our cohort, prevalent hypoalbuminemia, intervening hypophosphatemia, and ultrafiltration may have contributed to alkalosis. Unfortunately, we did not have data about our ability to mimic kidney function; therefore, the relative ionic concentration, yet homeostasis of the entire body is not determined. What is the overall driver of this physiologic necessity? Classic renal physiology looks at acid-base balance in terms of hydrogen ion generation and excretion, yet potentially, this model does not reflect the underlying regulatory mechanism (4). Routine therapy monitoring parameters do not look at the overall balance of ions (particularly, chloride) which potentially could be a fundamental driver. It is remarkable that after more than 40 years of tinkering with dialysis, we have more basic questions about our ability to mimic kidney function.

Figure 1. Mean serum chloride, SID apparent and SIG when pH > 7.45 per day of CRRT. SID apparent = [Na+] + [K+] + [Mg2+] + [Ca2+] – [Cl–]; SID effective = 2460 × 10–11 × PCO2/(10–4) + [albumin] × (0.123 × pH – 0.631) + [phosphate] × (0.309 × pH – 0.469); SIG = SID apparent – SID effective. CRRT, continuous renal replacement therapy; SID, strong ion difference; SIG, strong ion gap.

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The value of procalcitonin to diagnose infection in critically ill patient: caveat emptor!

To the Editor:
We read with interest the article by Amour et al. (1) on the influence of renal dysfunction on the accuracy of procalcitonin (PCT) for the diagnosis of postoperative infection after vascular surgery. The authors convincingly demonstrated that in patients with acute kidney injury (AKI), PCT tends to be more elevated and they suggest that in these patients, different cutoff levels are to be used for the diagnosis of infection.

In their conclusion, the authors also state that PCT is accurate to diagnose postoperative infection, but the figures reported in the manuscript may suggest otherwise. The area under the receiver operating characteristic curve of the maximal level of PCT is reported to be 0.70 (95% confidence interval 0.60–0.80) and using the optimal cutoff of 0.8 ng/mL, derived from the receiver operating characteristic curve, the sensitivity and specificity reported are 0.79 and 0.67, the positive predictive value 0.43, and negative predictive value 0.91. Although these may be better than the predictive values of other biochemical parameters (unfortunately no comparison was made in the article), they are still worse than the performance of the clinician (see Table 4 of the original article), and therefore we believe that the use of PCT has only limited value when translated into clinical practice. If PCT would have been used (using the optimal cutoff of 0.8) to initiate antibiotics, this would have resulted in unnecessary administration of antibiotics in more than half of the patients (positive predictive value 43%), a figure which seems unacceptable in times of increasing antibiotic resistance partly because of injudicious use of broad-spectrum antimicrobial agents (2).

The authors found that PCT is an earlier marker of infection as the maximal concentration preceded the clinical diagnosis of infection (assessed using the initiation of antibiotics by clinicians as the moment of diagnosis), whereas the expert panel determined that the start of the infection was in fact one day earlier. Figure 4 in the article shows the evolution of PCT in patients with and without infection and clearly shows that at the moment of diagnosis of infection by the expert panel, mean PCT levels were below 1 ng/mL; only one day later, at the moment that clinicians had started antibiotics without knowledge of PCT levels, PCT levels were indeed maximal, and above the 0.8 ng/mL cutoff in the majority of the patients. The conclusion that PCT is an early marker of infection is not supported by the data in the manuscript as it was only on the day of clinical diagnosis that the levels were above the threshold. As such PCT did not add value to the diagnosis of sepsis as based on classic signs of systemic inflammation (3).

The question remains whether PCT can help us to differentiate between inflammation and infection. The data presented in this study nicely illustrate that PCT is also increased in patients with inflammation of noninfectious etiology. Control patients with AKI have normal PCT levels before surgery, but have increased PCT levels after surgery compared with non-AKI patients. This suggests that the higher PCT levels in AKI patients are just an illustration of the increased inflammatory response in AKI patients with infection (4).

Although PCT is often cited as a new exciting tool to diagnose infection (5), a recent review of the diagnostic accuracy of PCT to diagnose infection in critically ill patients found that the diagnostic odds ratio of PCT to diagnose infection was poor, and the summary receiver operating characteristic curve of all studies reported to be 0.78, indicating that the performance of PCT was low (6). The values reported in the manuscript by Amour et al. are comparable at best and in our opinion the above considerations limit the use of PCT to diagnose infection and to guide antibiotic treatment in severely ill patients.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

To the Editor:
We thank Dr. De Waele et al. for providing us another opportunity to demonstrate that procalcitonin (PCT) is at this time the most efficient marker available in the market for the diagnosis of postoperative infection despite the fact that it is not the “ideal” marker. The superiority of PCT compared with other markers such as C-reactive protein, leukocyte count, or interleukin-6 or -8 has been
well established, (1, 2) and we confirmed in this study that PCT is independent of the perioperative inflammatory response in contrast with what De Waele et al. claimed above. As shown in our study, (3) the incidence of the postoperative infection was important (24%) after major vascular surgery while PCT value was increased early (1 day before onset of infection, p < 0.05). In contrast, effective treatment of infection was delayed (1 day after onset of infection, p < 0.05) because of the complexity for the physician to make the diagnosis of infection in the perioperative period. We do not think that it is appropriate to say that PCT is of no value because its diagnostic accuracy is not better than that of the physician who knows the whole story and looks at many other diagnostic tests (body temperature, chest radiograph, leukocytes, etc . . .). In our study, after adaptation to temperature, chest radiograph, leukocytes, etc., many other diagnostic tests (body temperature, chest radiograph, leukocytes, etc . . .). In our study, after adaptation to temperature, chest radiograph, leukocytes, etc . . .).

In conclusion, the rise of serum PCT level adapted to renal function in the postoperative period of major vascular surgery should alert the physician and should help him/her to decrease the delay of treatment of postoperative infection, independent factor of morbidity in critically ill patients. In conclusion, the key message of our study was elsewhere: acute renal dysfunction modifies PCT levels and, thus, must be taken into account.

The authors have not disclosed any potential conflicts of interest.

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Right data, right conclusions
To the Editor:
In the accompanying editorial to our article on red blood cell transfusion (RBCT) and cerebral oxygenation in patients sustaining severe traumatic brain injury (1), Netzer et al. (2) claimed that our data do not support our conclusions. We would like to address the several concerns raised by Netzer et al. (2) regarding the validity of

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our results. First, the exclusion of one third of patients was justified by the need of obtaining a homogeneous patient sample, which enabled us to perform a reliable evaluation of the influence of the length of blood storage on brain oxygenation. Second, traumatic brain injury patients have a higher critical cerebral brain flow threshold for the development of irreversible tissue damage (15 mL·100 g⁻¹·min⁻¹) than other neurocritical patients (3), and anemia might reduce cerebral PbrO₂ and increase cell death, as recently demonstrated in experimental traumatic brain injury in rats (4). In many centers, traumatic brain injury patients are currently transfused to maintain hemoglobin around 10 g/dL (5), and it has been demonstrated that increasing hemoglobin from 8.7 to 10.2 g/dL improves local cerebral oxygenation (6), whereas severe anemia (hemoglobin <8.5 g/dL) may worsen cerebral lesion in low-weight infants and patients with subarachnoid hemorrhage (7). Furthermore, low blood viscosity because of anemia might be deleterious because it causes vasoconstriction, and decreases blood flow, shear stress, and functional capillary density. In these circumstances, increasing blood viscosity by RBCT might favor maximal functional capillary density and oxygen transport to brain (8). Netzer et al. (2) also questioned the reliability of PtiO₂ for assessing the effects of RBCT. In this regard, despite being a local monitor, the obtained values of PtiO₂ can be extrapolated to evaluate global oxygenation when the PbtO₂ monitoring is performed in relatively uninjured brain, as it was carried out in most of our patients. Additionally, mean PtiO₂ in the pericontusional tissue is lower than PtiO₂ in the normal-appearing tissue, justifying the use of a higher transfusion threshold to increase TiO₂ to injured brain areas (9). Third, for red blood cells transfusion older than 19 days, mean storage time was 4 wks (29.2 ± 6 days) (1). This storage time allows for the RBC to lose all their 2,3-diphosphoglycerate and to decrease their adenosine 5’-triphosphate, thus explaining their incapacity to increase PtiO₂. Fourth, it seems that Netzer et al. (2) have recalculated the mean PtiO₂ increment for each time interval to demonstrate that transfusion of young RBC (<10 days) was associated with the smallest average increment. However, as shown in our article, within-group differences (i.e., differences between the PtiO₂ value at each observation time point with respect to baseline value) seem to be a more accurate way to demonstrate the presence of significant changes in PtiO₂ after RBCT. In addition, it is hardly probable that our results were influenced by between-group differences in baseline variables, as all four groups were homogeneous with respect to them, including Glasgow Coma Scale and Injury Severity Score (1).

We have previously demonstrated in a wide sample of patients that the RBCT-related increments in brain PtiO₂ were inversely correlated with the patient’s baseline PtiO₂ (10). Baseline PtiO₂ values in patients receiving blood stored for 10–14 or 15–19 days were equal or higher than in those receiving blood stored >19 days. However, in the first two groups, PtiO₂ values were significantly increased after RBCT, whereas no increment in PtiO₂ was observed at any observation time in the last group (1). Therefore, our data suggest that baseline oxygenation is not the only variable governing the efficacy of RBCT. However, in agreement with Netzer et al. (2), a control group with crystalloid or colloid infusion would have been useful to ascertain whether the increment in PtiO₂ resulted from the increase in the hemoglobin or in the intravascular volume.

Finally, prolonged RBC storage (>14 days) has been shown to increase the risk of postoperative complications and mortality in cardiac surgical patients, suggesting that it might also play a role in the poorer clinical outcome observed in critically ill patients receiving RBCT (11). On the other hand, an increase in oxygen consumption after RBCT has not been consistently shown (12), and this could be due to the lack of efficacy of stored RBC to increase tissue oxygenation. Our study (1) showed that RBCT increased cerebral oxygenation in >75% of transfused patients, just failing only in those receiving RBC stored >19 days. Therefore, in contrast with the opinion of Netzer et al. (2), our conclusions are supported by our results; i.e., right data, right conclusions.

The authors have not disclosed any potential conflicts of interest.

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It is the time, not the ratio

To the Editor:

Ward and Dushay (1) present an excellent review about mechanical ventilation in patients with respiratory failure caused by acute exacerbation of chronic obstructive pulmonary disease. We agree about the importance of reducing the dynamic hyperinflation caused by expiratory air flow obstruction. Ward and Dushay make clear that this is accomplished best by reducing the respiratory rate and that shortening inspiratory time to decrease...
The inspiratory to expiratory ratio (I:E) is of less importance. However, we believe that this statement should be rephrased and strengthened. In daily practice we see important errors made by misconception of the I:E concept. For example, with a fixed inspiratory time of 1 sec, reducing the respiratory rate from 20 to 10 breaths/minute would create an inspiratory time increase from 2 to 5 secs, the I:E ratio will be 1:5. If, with a respiratory rate of 20 breaths/minute, the I:E ratio will be set at 1:5, the expiratory time will become 2.5 secs and the inspiratory time 0.5 secs. With the same ratio, we have reached a completely different expiratory time. Therefore, focusing and targeting on the I:E ratio will not necessarily mean a clinically relevant increase in expiratory time and it will also decrease the inspiratory time. The latter is also of great importance in patients with chronic obstructive pulmonary disorder. With volume-controlled ventilation, it means an increase in required flow and subsequently a substantial increase in peak pressure to reach the same tidal volume. In pressure-controlled ventilation, it might lead to insufficient time for complete delivery of the tidal volume. The statement should, in our view, be rephrased as follows: hyperinflation can be diminished by extending the expiratory time. This can be accomplished by decreasing the ventilatory rate. Decreasing inspiratory time below 1 sec has no clinically relevant effect on expiratory time and can lead to difficulty in delivering the required tidal volume. The I:E ratio has no clinical relevance and should not be used as target in ventilator tuning.

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Meta-analysis under the spotlight: We must differentiate its limitations versus its prejudices

To the Editor:

“There are lies, damn lies, statistics, and ‘in my clinical experience’.” Lloyd D. Fisher (1)

I would like to congratulate Drs. Tobin and Jubran (2) for their excellent article recently published in Critical Care Medicine.

I fully agree with the authors that although a meta-analysis has the great capability to increase the precision of several trials, it does not mitigate the presence of systematic errors from the same studies.

I also agree with the fact that the American College of Chest Physicians Task Force missed the opportunity to address the reasons for heterogeneity among the trials and made conclusions without addressing the potential presence of important systematic errors.

On the other hand, it seems that the authors decided to use their critique against the Task Force’s conclusions as a reason to also critique the meta-analysis methodology. Although this approach may seem to be logical, Tobin and Jubran fell victim to their own prejudices against meta-analyses.

First, Tobin and Jubran (2, 3) failed to recognize that what they both did in their recent publications about weaning-predictor tests is nothing more and nothing less than a classic systematic review and meta-analysis! More specifically, this was a Bayesian meta-analysis. This is really important because the authors carefully avoided the use of the term “meta-analysis” in their two articles, but they were obviously betrayed by their own statistical methodology and pooled results, which are emblematic of the meta-analytic methodology.

Second, Tobin and Jubran failed to recognize that disregarding evidence from other ventilator weaning studies because of the potential presence of systematic errors is as inappropriate as excluding already enrolled patients from clinical trials after the randomization process has taken place. That is, if the study meets the meta-analysis inclusion criteria, the study must be included, and once the analysis takes place, then the authors will look for the differences in trial designs, systematic errors, and heterogeneity. Not the other way around.

Third, Tobin and Jubran failed to recognize that not performing a meta-analysis because the data are heterogeneous is in direct contradiction with the core of Bayesian philosophy, which was the methodologic basis for both their articles (2, 3). Bayes’ methodology depends on the explicit recognition of all available evidence (priors) to be analyzed with the empirical evidence (Bayes factor) in order to have a posterior probability. In analogy, no good clinician will use a sole diagnostic test as the only clinical tool to wean a patient from the ventilator. All clinical evidence is gathered by the bedside clinician before such an important decision is made, and that includes numerous variables based on the patient’s current clinical picture. In the same way, a diagnostic meta-analysis gathers all available evidence to better understand and precise the usefulness of different diagnostic tests (4). If the authors believe that the priors should not be used to better understand the empirical evidence (i.e., they do not agree with the Bayesian assumptions), they should not perform any of the Bayesian meta-analyses done in their articles from the very start.

Fourth, Tobin and Jubran failed to recognize that traditional (narrative) review articles are even more prone to flaws than systematic reviews and meta-analyses. A systematic literature review is an obligatory and standard part of any meta-analysis. Traditional reviews are not usually systematic, so the authors commonly select studies that support his/her views. Consequently, traditional reviews are notoriously laden with the authors’ own “pride and prejudices” without any safeguards to protect the readers against them. Furthermore, traditional reviews simply count and describe the studies supporting different sides, completely ignoring the sample size, data variance, and treatment effect size, which can only be done by the performance of a systematic search and meta-analysis. All these prejudices are commonly taken as final truth by many clinicians because the traditional reviewer is frequently an “expert” in the field. Although this can also occur in a poorly executed meta-analysis, this is rare because it is already a universal publication requirement for meta-analyses to have not only the qualitative (p values), quantitative (I-squared) degrees of heterogeneity, and adjustment for variance (fixed and random-effects models) explic-
ibly reported, but also a sensitivity analysis based on the different trial designs and potential reasons for heterogeneity, such as the presence of systematic errors. One great example to understand the differences between traditional and meta-analysis reviews is concerning the use of thrombolytics for patients with myocardial infarction. A systematic review and meta-analysis done in 1992 (5) demonstrated strong evidence that thrombolytic drugs were already beneficial in acute myocardial infarction since 1977, about 14 years before the first large confirmatory trial! A systematic search I performed (available upon request) with our librarian, Dr. Cynthia Schmidt, yielded 531 traditional reviews (excluding the duplicated reports) published during those 14 years. I would have to ask the Journal of Critical Care Medicine editors for unlimited space to cite this incredible number of traditional reviews written by so many experts, which obviously had zero impact on the clinical use of thrombolytics in myocardial infarction for the long 14 years.

Fifth, Tobin and Jubran failed to recognize that money is generally not an issue that differentiates traditional from meta-analysis reviews. They stated that “...a major difference between systematic reviews and traditional review articles is money.” This is not the reality that my colleagues and I myself know. The largest and one of the most reliable meta-analyses database in the world, The Cochrane Library, provides high-level education about meta-analysis methodology free of charge, excellent statistical software to execute these studies free of charge, peer-reviewed evaluation of meta-analysis protocols free of charge, and, if the final study is accepted, open-access publication free of charge. It is no wonder why Tobin and Jubran did not provide any scientific evidence to support their statement that money is the major driving force for scientists to perform meta-analyses. I believe that if grants could be more widely applied to researchers who are using the meta-analytic methodology in their research, we would have additional high-quality meta-analyses and more refined statistical methodologies at this time.

Sixth, Tobin and Jubran failed to recognize that the comprehensive search for the causes of trials’ heterogeneity is in itself a scientifically valid and legitimate reason to publish a meta-analysis. Dr. Greenland, the epidemiologist, goes even further and states that “…the primary value of meta-analysis is in the search for predictors of between-study heterogeneity…” (6). The meta-analysis by Tobin and Jubran is an example of the value of this methodology to better understand the differences among trials and their effect on clinical outcomes. Interestingly, when Dr. Tobin was the editor for the American Journal of Respiratory and Critical Care Medicine, he not only accepted one of the most controversial meta-analyses recently done in critical care medicine (7), but also wrote a full three-page editorial to explain his decision (8). Ironically, that same meta-analysis was also plagued by the famous “heterogeneity” problems with which Dr. Tobin criticized so much in his new article (2). However, instead of simply disregarding all trials and not performing a meta-analysis, Eichacker et al. (7) chose to pursue an in-depth scientific investigation of the reasons for that, and directly addressed the heterogeneity by appropriate scientific reasoning and meta-analytic methods. Hence, I assume that Dr. Tobin accepted that manuscript because it was a high-quality meta-analysis that brought important new insights to the management of patients with acute respiratory distress syndrome.

Seventh, Tobin and Jubran stated in their conclusion that “If authors were to submit a manuscript based on an original research study that contained the systematic errors included in the Task Force meta-analysis (selection bias, misclassification bias, and confounding), a conscientious reviewer would instantly recommend rejection.” Dr. Tobin, as a previous editor of a journal, should know better than most of us that if he would reject all articles with “selection and misclassification bias, and confounding,” he would not have survived as a journal editor for more than a few weeks, simply because the only articles he would be able to accept (to avoid these biases) would be high-quality randomized, double-blinded trials! Interestingly, these randomized trials have been the clear minority of the articles that Dr. Tobin accepted as the editor of the American Journal of Respiratory and Critical Care Medicine. We need to be realistic. There are uncountable examples of studies which are flawed by Dr. Tobin’s requirements (e.g., retrospective and prospective observational, retrospective and prospective case-control, historical and prospective cohort, randomized unblinded studies, and even randomized double-blinded trials), but that have changed medicine for better and forever. If we will have to wait for the completion of perfect randomized double-blinded studies for every single diagnostic and therapeutic approach before their bedside application, we will do a great disservice to our patients.

Finally, I would like to disclose that I myself have performed and published meta-analyses (9, 10), by the way, without any funding! Also, I have not participated as a member or consultant for the American College of Chest Physicians Task Force. Although I personally believe that meta-analyses have a solid place in our current clinical research times, I also recognize that meta-analyses are not a panacea for finding the scientific truth, and have several limitations, as pointed out by Tobin and Jubran. It is well known that meta-analysis results may not later be confirmed by large trials (11). It is also well known that even large high-quality randomized clinical trials may disagree among themselves. A classic example is the case for the benefits of magnesium in myocardial infarction observed by a meta-analysis (12), but not confirmed by a randomized trial (13). Two later studies demonstrated that the authors of the meta-analysis failed to recognize substantial publication bias (14), and that the prior assumptions were just not clinically realistic (15). Hence, the data may be of high quality, but if the methods are not of high quality, the results of the meta-analysis will not be reliable. Another reason for these differences between meta-analysis and large trials is simply due to the absence of enough evidence to reach a firm conclusion (in that case, a meta-analysis can also assist researchers to better design and power the next trial). That is why we still see (and will continue seeing) discordances between meta-analyses and clinical trials. These meta-analyses’ issues are absolutely the same as the ones seen for every type of study done in the field of medicine—poor design and/or poor methodology yield less reliable results. This is not to say (or to be misinterpreted) that we should be compliant with low-quality studies, but that study limitations are inherent in all medical sciences, without exception. Furthermore, we have ethical obligations to the patients who already volunteered to participate in all these “biased” studies. We cannot completely disregard these studies (or reject their publication) solely because they have biases. The in-depth understanding of biases and heterogeneity
within and between studies remains a critical mission for researchers working with the meta-analytic methodology. Even a meta-analysis with solid negative results should be quite useful to medicine—Dr. Naylor puts well that “The concept of failed meta-analysis is a straw man, for failed meta-analysis may be highly successful in meeting diverse information needs in modern health care” (16).

Therefore, one should always consider that the quality of a meta-analysis is directly related to three principal factors: 1) the quality of the available evidence; 2) the quality of the methodologic approach used by the researchers; and 3) the researchers’ intimacy with the clinical subject being meta-analyzed.

I conclude this article with Dr. Tobin’s own words that one of the views about scientific controversy “…sees controversy as a sign of vitality, emphasizing the importance of a subject.” (8) The important subject here happens to be meta-analysis.

The author has not disclosed any potential conflicts of interest.

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REFERENCES


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Is it too early to recommend a restrictive transfusion strategy in critically ill patients with ischemic heart disease?

To the Editor:

We wish to thank Dr. Gerber for his interesting review of red blood cell transfusion strategies in critically ill patients with ischemic heart disease (IHD), acute coronary syndromes, and undergoing cardiac surgery (1). The current evidence supports the assertion that young healthy individuals without coronary artery disease do not benefit from a liberal transfusion (2).

However, in the noncardiac surgery intensive care patient with IHD, retrospective studies have demonstrated that anemia increases morbidity and mortality and red blood cell transfusion seems to ameliorate these risks (3, 4). It has been suggested that the prospective transfusion requirements in critical care (TRICC) trial (2) and the subsequent post hoc analysis, centered on the patients with IHD (5) provide evidence that a restrictive transfusion strategy (hemoglobin target 7–9 g/dL) is safe and should be recommended. However, there are a number of caveats with both the study and the conclusions drawn that we feel should make the intensive care physician think carefully before managing patients with IHD with a restrictive red cell transfusion strategy. First, only 20% of the patients recruited into the TRICC trial had IHD, compared with the 26% of patients excluded by recruiting clinicians/family indicating the potential for selection bias. Second, in the post hoc analysis of patients with IHD (5), there was a trend to lower mortality in the liberal transfusion group compared with the restrictive group. Furthermore, Deans et al. (6) recently showed that the effects of the differing transfusion strategies on 30-day mortality in the TRICC trial were significantly different and opposite depending on the presence or absence of prerandomization IHD (Breslow-Day test; p = 0.03): patients with IHD randomized to the restrictive strategy group had an increased mortality compared with the liberal transfusion strategy (6). Finally, the TRICC trial was conducted before universal leucodepletion of red cell products in Canada. Leucodepleted red blood cells currently used in many countries have a lower transfusion risk profile compared with the older non-leucodepleted products (7), a feature that may have confounded the results of the TRICC study.

In summary, it may be too premature to advocate a change in clinical practice and the use of a restrictive strategy in critically ill patients with IHD. In the absence of a randomized controlled trial specifically designed to answer this question in these patients, clinicians would be well-advised to carefully apply clinical judgment, assess the signs and symptoms of anemia and consider the perceived balance between the degree of IHD and myocardial oxygen demand, and the risks and benefits of red cell transfusion.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES

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The author replies:

I would like to thank Dr. Nichol and his colleagues for their interest in this topic and their insightful comments. The analysis of the data presented in the Transfusion Requirements in Critical Care (TRICC) trial, as performed by Deans et al. does indeed raise the possibility that factors such as recruitment bias and patient allocation may have impacted outcomes in that study (1, 2). It is certainly true that in the TRICC trial recruitment may have been affected by clinician judgment, and that as a fixed therapeutic trial patient allocation may have suffered from the potential confounding effects of having subjects randomized “inappropriately” to receive treatments which they do not require, such as may have been the case with younger, relatively healthier patients being randomized to the liberal transfusion arm. The findings by Deans et al. identified differing effects of transfusion strategy on mortality depending on the presence or absence of prerrandomization of ischemic heart disease. It is pointed out that the impact of transfusion on mortality is different and opposite depending on pre-randomization status regarding the presence of ischemic heart disease when evaluated by the Breslow-Day test. However, there remains no specific statistical evidence that within the group of patients with ischemic heart disease, a more liberal strategy confers any advantage, based on the data available from the TRICC trial (3).

If the TRICC data were the only evidence suggesting that transfusion is, in a large proportion of cases, ineffective and possibly detrimental even in the face of active coronary ischemia, it would be easier to more readily dismiss these conclusions. However, as noted in my review, numerous subsequent although primarily retrospective studies involving many thousands of patients have arrived at a similar conclusion, particularly in the setting of non-ST elevation acute coronary syndrome (4).

The possible presence of leukocytes in transfused red cells in some of the previously reported studies and possible impact of leukoreduction on improved outcomes is an open question. Although the data reported by Hebert et al. (5) demonstrated a small but significant reduction in the mortality rate after the introduction of a universal leukoreduction program in Canadian blood banks, the rate of infection was not decreased. The potential implication for the cardiac population is uncertain and speculative at this time.

It is not surprising, given the well established relationship between anemia and worse outcomes in coronary artery disease that there remains a high degree of skepticism toward a restrictive transfusion strategy in these patients. However, in the face of an extensive body of literature demonstrating the limited efficacy of stored red blood cells to deliver oxygen at the cellular level and mounting evidence that such blood has deleterious effects in variety of patient populations, it is not unreasonable to think that although anemia may be bad for patients with ischemic heart disease, transfusion may not necessarily offer them effective treatment and may adversely affect cardiac patients as well.

I would agree that ideally a prospective trial of transfusion in the setting of acute coronary ischemia would clearly be the best way to answer the question at hand. Careful clinical judgment is indeed essential to appropriate decision making, but must be predicated upon the best available evidence. At the present time, I still believe that this evidence continues to suggest that a relatively restrictive utilization of packed red blood cells is the best supported approach to this population.

The author has not disclosed any potential conflict of interest.

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REFERENCES
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Relationships between fever and outcome in intensive care unit patients

To the Editor:

We read with great interest the article by Laupland et al. (1), a large, retrospective, multicenter study on the association between fever and outcome in intensive care unit patients. Although we appreciate the important information presented in this article, we wish to comment on some associated issues.

First, temperature elevation has been associated with worse neurologic outcome and increased mortality in traumatic, ischemic, or hemorrhagic cerebral damage patients (2–3). In the study by Laupland et al., these patients were included in the trauma/neurologic category; however, their exact number has not been reported. Unless the percentage of cerebral damage patients was very small, the finding that mortality was
significantly lower in trauma/neurologic patients manifesting (admission or subsequent) fever is unexpected and difficult to interpret.

Second, the findings of previous studies (4, 5) associating fever with significantly higher mortality of critically ill patients were not confirmed in the study by Laupland et al. We have prospectively evaluated the association between fever and mortality in a medical-surgical intensive care unit (6) and found that crude intensive care unit mortality was higher in febrile patients (34.5% vs. 18.7%, \( p = 0.022 \)). However, fever was no longer associated with mortality after adjusting for patient severity (\( p = 0.384 \)). Our opinion is that the higher mortality among febrile, critically ill (excluding cerebral damage) patients mainly reflects patient severity caused by coexisting comorbidities (infection, myocardial infarction, etc.), rather than a detrimental effect of fever per se.

Third, in agreement with Laupland et al., we reported that high fever was associated with significantly higher mortality (19% with peak temperature 38.3°C–39.2°C, 100% with peak temperature >40.2°C) (6). Furthermore, peak temperature remained an independent predictor of mortality (after controlling for age, infection, and severity) in our study (\( p < 0.001 \)) (6) and in a surgical intensive care unit study (\( p = 0.003 \)) (5) even after patients with cerebral damage were excluded. Because these findings imply that high fever may be a mortality mediator, we would be interested to know if Laupland et al. observed that peak temperature (irrespective of fever onset) is independently associated with mortality in each diagnostic category.

Although this study adds valuable information to our clinical understanding, questions such as if the suppression of high fever may act protectively and therefore improve outcome, remain to be answered. Thus, appropriately designed, prospective randomized trials are required for defining patient groups likely to benefit from antipyretic treatment, the threshold for initiating this treatment, and whether antipyretic drugs should be combined with physical antipyresis.

The authors have not disclosed any potential conflicts of interest.

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Why sedation protocol did not work

To the Editor:

We read with interest the article by Bucknall et al. (1) in which the authors evaluated the effectiveness of protocol-directed intensive care unit (ICU) sedation for mechanical ventilation within a closed Australian ICU.

The use of a sedation protocol has been recommended (2), and sedation protocols have demonstrated effectiveness in improving sedation practice and ICU outcomes (3). Consequently, sedation practice has changed to favor increased use of sedation protocols. Randomized controlled trials, inside and outside North America, have evaluated the effectiveness of protocol-directed sedation.

The investigators proposed several explanations for the lack of benefit of a sedation protocol, including noncompliance with the protocol and the model of ICU medical and nursing coverage. Other explanations should also be considered. First is the issue of contamination. Because of the unblinded nature of the trial and to the training given to all nurses, it is possible that nurses were indirectly implementing the protocol even in the control group patients (education effect). We have seen similar findings in a similarly designed trial in our center in which no significant differences were observed between the protocol and control groups (4). One possible way to avoid contamination is to use a before–after study design. Second, a protocol is a means to direct management; however, alone it does not guarantee success or improvement in outcome. In our study, we found significant improvement in sedation practices after 3 months whether patients are in the protocol or in the control group suggesting that the education and feedback program rather than the direct effect of the protocol are responsible for most of the observed effects (4). Third, because of institutional differences in organization (e.g., nurses may automatically titrate and wean sedatives/analgesics, twice daily intensivist-directed medical rounds, and 24-hr house medical staff), the major component of the protocol, which is weaning, was applied in the control group. Fourth, although sedation scales are used, assessment of sedation remains subjective, and validated objective tools are still lacking, resulting in difficulty in discriminating between degrees of sedation and thus confounding the successful implementation of any sedation protocol.

In a recent article, the author reported (5) that questionnaires distributed to multidisciplinary team members, who had used a sedation protocol, caused staff to perceive sedation management to be enhanced with the use of a protocol, and she recommended that it be incorporated into routine clinical practice. She also reported a perceived improvement in patient outcome, including a decrease in frequency of oversedation resulting in a reduced ICU stay. Furthermore, the author suggested introduction of other interventional protocols where variability in clinical decision making exists.

We agree with the investigators that sedation practice varies between countries, and a protocol in one institution may not be appropriate for another organization with a different patient population. Guidelines aid in the development of local protocols which should be customized to suit patient populations and institutional preferences. However, this study does not conclusively exclude benefit of sedation protocols and its results must be interpreted after considering the points mentioned above.

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The authors reply:

International evaluations of sedation protocols have demonstrated variable patient outcomes that have been attributed to both research validity and research context (1). In their letter to the editor, Haddad et al. (2008) reinforce our previously highlighted study limitations and also concur with our recommendation for caution in transferring international research findings without prior customization for the local context.

In discussing alternative research designs, Haddad et al. propose a before-and-after approach. Despite the possibilities for bias inherent in unblinded studies, we continue to prefer random allocation of patients in evaluation of an intervention rather than nonrandomized studies with historical controls. Nonetheless, another Australian study using a before-and-after design found similar results to ours, suggesting that contextual differences may be more influential on patient outcomes than the effect of specific sedation protocols (2).

We argue that quality differences in organizations may be influenced strongly by staff characteristics (1). The majority of Australian intensive care unit nurses are baccalaureate-prepared registered nurses with postgraduate qualifications in critical care, educated in patient ventilation, and sedation management. These nurse characteristics and the model of care (1 nurse:1 patient ratio, intensivists as primary physicians, 24-hr house medical staff, twice daily interdisciplinary ward rounds including a pharmacist and physiotherapist, and ventilation monitoring by nurses) may have rendered redundant any advantage of the protocol. That is, if unit sedation levels already approximated current best practice, there may have been limited scope to reduce ventilation duration further in response to a sedation management intervention. Indeed, Haddad et al. suggest that education and feedback were responsible for improved patient outcomes in their own study, rather than the sedation protocol.

We agree with Haddad et al. that even when evidence-based protocols are in place they do not guarantee evidence-based practice. Many factors influence the uptake and adherence to guidelines, including clinician perception of the guideline. As we report, a survey of staff perceptions of the sedation protocol and its use (3) was undertaken before commencing our reported randomized control trial, which documented generally positive staff attitudes to the possibility of a sedation protocol. Rose and Bucknall (3) do not recommend the protocol be incorporated into routine practice as Haddad et al. mistakenly report but instead recognize that positive perceptions may assist with adoption of a protocol.

An important consideration in intervention research is the ability to discriminate sufficiently between intervention arms. We did so by comparing usual care, where no scoring system was in place and the sedation management was individualized, against a protocol where a scoring system was used, a target score set and sedation standardized by protocol. We agree that our failure to demonstrate a sedation protocol effect may also be due to the subjective nature of the scoring system and its inability to discriminate changes in clinical conditions (1, 4). Nonetheless, we believe that close observation and an ability to recognize subtle changes in a patient’s level of sedation, with the aim of minimizing sedation and delivering the required treatments, is likely to be at least as effective as protocol-directed sedation.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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Fever in critically ill patients

To the Editor:

We read with great interest the excellent and comprehensive guidelines for evaluation of new fever in critically ill adult patients (1). The authors review with precision different infectious and noninfectious etiologies of fever. In the noninfectious causes, they show up important febrile syndromes associated with drug use such as malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome or associated with withdrawal of certain drugs like alcohol, opiates, barbiturates, and benzodiazepines. However, the levodopa-withdrawal syndrome is not mentioned in the
The authors have not disclosed any potential conflicts of interest.

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safety of the procedure (3). Most importantly, life-threatening bleeding was not reported in any of the respective investigations.

We totally agree with Wolfrum et al. in that acute myocardial infarction patients undergoing MTH should be observed carefully for bleeding complications (especially in the early phase) and believe that the combination of MTH with percutaneous intervention and respective medication may be considered safe. Although concerns for bleeding complications should at this point in time not lead to withhold MTH treatment, it will be necessary to perform large-scale analyses investigating bleeding complications and other potential side effects such as prolongation of mechanical ventilation or increased rates of infectious complications. However, when looking at the side effects of MTH, it seems important to remember the undisputed beneficial impact of the procedure on neurologic outcome of patients with out-of-hospital cardiac arrest which—at this point in time—clearly seems to outweigh potential complications.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


The authors reply:

We thank Schefold et al. for their thoughtful comments on our study on the combination of mild therapeutic hypothermia (MTH) and acute percutaneous coronary intervention in patients with ST segment elevation myocardial infarction and consecutive cardiac arrest (1). Schefold et al. discuss that MTH may activate several mechanisms potentially leading to bleeding complications in such patients. Indeed, in the Hypothermia After Cardiac Arrest trial (2) and our study (1) there was a tendency for increased bleeding complications in MTH-treated patients as compared with controls. Our patients were at particularly high risk for bleeding because all received aspirin, clopidogrel, and therapeutic doses of unfraccionated heparin in the setting of 6–7 French arterial sheath placement in the right groin. A larger proportion of our MTH patients than of our historical control patients received a glycoprotein IIb/IIIa receptor antagonist (94% vs. 71%) which might have contributed to our observation. However, these differences in bleeding complications were still present when the groups were adjusted to the use of antiplatelet agents.

Some other groups also investigated the combination of MTH and acute percutaneous coronary intervention, but interpretation of the results is also limited because of the small sample size. In the study of Schefold et al. (3), the rate of bleeding complications was lower than in our study and the authors did not observe a difference as compared with a historical control group without MTH. Unfortunately, in the study of Knaefel et al. (4), who included 40 ST segment elevation myocardial infarction patients undergoing MTH and acute percutaneous coronary intervention, bleeding complications were not reported in detail. Therefore, we agree with Schefold et al. that future studies and registries should focus on bleeding complications in patients treated with MTH. Particular attention should relate to the definition of “bleeding” in this context (5). We also want to affirm that, as a result of the existing studies, the benefit of MTH on mortality and neurologic outcome clearly exceeds the potential harm of bleeding complications.

The authors have not disclosed any potential conflicts of interest.

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REMARKS


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Acute alcohol withdrawal as a risk factor for intensive care unit–acquired infection

To the Editor:

I read with interest the article by Gacouin et al. (1). The authors found at-risk drinking to be a significant risk factor for intensive care unit (ICU)–acquired infection, and for ventilator-associated pneumonia. Immunologic and nonimmunologic factors were suggested to explain these results, including malnutrition, poor dental hygiene, suppression of normal cough, and abnormal host immune response. In fact, previous studies demonstrated that chronic alcohol consumption was associated with abnormalities in immune function (2). However, another potential explanation for the association between at-risk drinking and higher rates of ICU-acquired infection is acute alcohol withdrawal at ICU admission.

A recent study compared rates of postoperative pneumonia between long-term

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3131

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alcoholic and nonalcoholic patients (3). The authors found significantly higher rates of postoperative pneumonia in long-term alcoholics compared with nonalcoholic patients (54% vs. 26%, p = 0.03). After surgery, a significant suppression of the cytotoxic T-lymphocyte type 1:type 2 ratio, the interleukin-10 ratio from lipopolysaccharide-stimulated whole blood cells, and a significant increase of plasma interleukin-10 was observed. The authors concluded that this altered cell-mediated immunity might have accounted for the increased infection rate in long-term alcoholics after surgery. Disturbances of the stress axis and hypercortisolism were reported to have a major impact on infections (4). Further, disturbances of the automatic nervous system and of the hypothalamic-pituitary-adrenal axis were found in long-term alcoholic patients with acute alcohol withdrawal without prior surgery (5). One could argue that in long-term alcoholic patients, admitted to the ICU with acute alcohol withdrawal, higher rates of ICU-acquired infection might be related to disturbances in stress axis. Unfortunately, in the study by Gacouin et al. (1) no information is given on acute alcohol withdrawal. Could the authors provide the rate of long-term alcoholic patients with signs of acute abstinence? Was the rate of ICU-acquired infection higher in patients with signs of acute alcohol abstinence compared with patients without signs of acute abstinence? What was the duration between ICU admission and first ICU-acquired infection?

In their accompanying editorial, Yost and Grooper (6) stated that many physicians treat patients at risk for alcohol withdrawal with prophylactic doses of benzodiazepines. They suggested that sedation of at-risk drinkers might have prolonged duration of mechanical ventilation and increased the risk for infection. However, a recent randomized study aimed to evaluate the impact of intervention at the level of the hypothalamus-pituitary-adrenal axis on postoperative pneumonia rate in chronic alcoholics (7). One hundred twenty-two consecutive patients undergoing elective surgery were randomized to receive ethanol, morphone, ketoconazole, or placebo on the morning before surgery and for 3 days after surgery. All interventions significantly decreased postoperative hypercortisolism and prevented impairment of the cytotoxic T-lymphocyte type 1:type 2 ratio. All interventions decreased pneumonia rate from 39% to a median of 5.7%. Could the authors provide the number of at-risk drinkers who received sedatives to prevent alcohol withdrawal? What was the impact of such a treatment on ICU-acquired infection rates? Further randomized studies should determine whether intervention at the level of the neuroendocrine-immune axis could reduce ICU-acquired infection rate in long-term alcoholic patients.

The author has not disclosed any potential conflicts of interest.

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REFERENCES


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The need for adequate rate control points to amiodarone as the drug of choice for treating critically ill patients with acute onset atrial fibrillation

To the Editor:

I read with interest the recent systematic review by Kanji et al. (1), which reported that clinical trials evaluating rhythm conversion of new onset atrial fibrillation in critically ill populations outside of cardiac surgery are lacking.

Although there is a significant body of evidence on the treatment of acute onset atrial fibrillation in the general hospital patient population, almost all of the published trials exclude subjects with critical illness or hemodynamic compromise.

The evidence from these trials points overwhelmingly in favor of the use of class IC agents, such as flecainide and propafenone in the stable patient population and amiodarone in patients with structurally or functionally abnormal hearts (2).

As the noncritical care literature demonstrates, a spontaneous sinus conversion rate of up to 76% within 24 hrs in patients with acute onset atrial fibrillation and as mortality data are never published in such trials, it could be argued that there is no evidence to show that active pharmacologic rhythm conversion is the optimum strategy in such subjects (3).

As rate-related cardiomyopathy is probably more important than the loss of atrial transport in the reduction of cardiac output in atrial fibrillation a rate control strategy while underlying precipitating causes are treated can be considered a valid way to manage these patients (4).

In addition, the Atrial Fibrillation Follow-up Investigation of Rhythm Management, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation, Atrial Fibrillation: Pharmacological Intervention in Atrial Fibrillation, Strategies of Treatment of Atrial Fibrillation, and How to Treat Chronic Atrial Fibrillation multicenter trials have shown that in patients with chronic atrial fibrillation there is no mortality benefit to sinus conversion over good ventricular rate control (5).

An ideal pharmacologic antiarrhythmic agent for use in acute onset atrial fibrillation on the general intensive care unit would combine rapid rate control effects with a good acute safety profile and a low risk of precipitating ventricular tachyarrhythmias.

In my opinion, the agent that best fits the above description is amiodarone.

Now, we just need some good evidence. The author has not disclosed any potential conflict of interest.

Jonathan Walton, Freeman Hospital, Tyne, United Kingdom
Parenteral vs. enteral nutrition?

To the Editor:

In the editorial “Death by TPN . . . the final chapter?” there are two comments disputing (1) recommendations that I have made regarding adequate glucose control and the relative risks and benefits of total parenteral vs. enteral nutrition in the critically ill (2). In the first instance, Marik states that in the era of tight glucose control the results of the observational study reported in the recent issue of Critical Care Medicine demonstrating increased use of parenteral nutrition in the more critically ill with increased mortality (3) invalidates our statement that infectious risk and mortality of parenteral nutrition can be overcome by tight glucose control. Although not different among the groups receiving parenteral nutrition only, enteral nutrition alone, the combination, or no nutrition in that study, the mean glucose control was approximately 180 mg/dL in each (3), which would not meet anyone’s definition of tight glucose control. In the second comment, Marik states that I am one of the two experts responsible for the “myth” that (1) enteral and appropriately administered total parenteral nutrition are equivalent (2). Although we do not have the definitive randomized trial to confirm this statement, the hierarchy of evidence in clinical research is the adequately powered randomized clinical trial, followed by the results gained through meta-analysis, both of which are far more powerful than observational studies with their inherent risks of residual confounding. Among meta-analyses, the individual quality of the trials included can dramatically influence the conclusions. Simpson and Doig, in their meta-analysis of enteral vs. parenteral nutrition in the critically ill included only studies in the critically ill and used only those with an intention to treat analysis indicative of the highest quality study (4). They found an approximate halving of mortality with parenteral nutrition despite an increased risk of infection. This difference was presumed due to late enteral feeding, because there was no mortality difference when early enteral was compared with parenteral (4). A subsequent meta-analysis comparing only early enteral to parenteral nutrition included some non-intensive care unit studies and confirmed these results of no mortality difference between the two and increased infective complications with parenteral nutrition (5) but certainly no mortality benefit from early enteral feeding. Finally, in a very large randomized trial of tight glucose control in critically ill patients adequately fed by enteral and/or parenteral nutrition, the improvement in mortality and infection rate was seen equally with both forms of nutritional support (6).

Thus, based on the highest quality of evidence presently available and until the definitive randomized trial is conducted, although early enteral nutrition may be preferred when possible, parenteral nutrition with tight glucose control in the critically ill should be considered the desirable alternative to late enteral or no feeding.

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REFERENCES


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