Review

Critical care of burn patients. New approaches to old problems

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A R T I C L E  I N F O

Article history:
Accepted 17 April 2015

Keywords:
Critical care
Burns
Treatment
New approaches

A B S T R A C T

Recent publications on treatment options in critically ill patients change beliefs and clinical behaviors. Many dogmas, which the modern management of critical illness relies on, have been questioned. These publications (consensus articles, reviews, meta-analysis and original papers) concern some fundamental issues of critical care: interventions in acute respiratory distress syndrome (ARDS), hemodynamic monitoring, glucose control and nutritional support and revise our views on many key points of critical care of burn patients.

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The complexities of dealing with critical illnesses brings to mind the mythic labyrinth of King Minos, full of hard choices, winding paths and multiple directions. Sometimes in our routine practice we try to correct certain parameters and bring them back to physiological levels, believing that their return to normal levels will help us to reverse the course of disease, forgetting that “physiological” is very different for different patients and for different clinical situations. Other times we look for complex solutions, when the actual solutions are much simpler than we had imagined. Occasionally we follow a particular path of dealing with clinical situations believing that only this path will obtain the best results and that other alternatives do not exist. The belief that there is only one right way to address various clinical situations is merely an illusion and this illusion does nothing but lead to conflict and confusion.

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http://dx.doi.org/10.1016/j.burns.2015.04.009
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Recent publications on treatment options in critically ill patients shook the world of critical care changing beliefs and clinical behaviors. Many dogmas, which the modern management of critical illness relies on, have been questioned. These publications (consensus articles, reviews, meta-analysis and original papers) concern some fundamental issues of critical care: interventions in acute respiratory distress syndrome (ARDS), hemodynamic monitoring, glucose control and nutritional support. These new changes can be divided into two groups expressed by the two parts of this ancient saying: ονεικ ἐν τῷ πολλῷ καὶ ἐν ἀλλῷ ἐν τῷ χρόνῳ πολῗ, more is not always better, but less is sometimes more.

1. More is not always better...

1.1. Glucose control

Acute illness is accompanied by the development of abnormal physiology which the clinicians monitor and attempt to correct believing that rapid correction and reversal of pathophysiological states will help to better patient outcomes. The pathophysiological changes, however, reflect the severity of the situation and their correction to perfectly normal levels does not always coincide with patient recovery. The concept of tight glucose control in critically ill patients could be mentioned here as a supporting example. The rigorous glucose control approach recommended previously also maintains the levels of glucose within normal range but conveys a risk of hypoglycemia and does not contribute to a better recovery of critically ill patients [1]. Hyperglycemia and insulin resistance in the setting of acute illness could be an evolutionarily preserved adaptive response that increases the host’s chances of survival; and attempts to interfere with this exceedingly complex multi-system adaptive response may be harmful [2]. Additionally, there is evidence that in patients with preexistent diabetes higher blood glucose levels during ICU stay were associated with lower mortality [3]. Glucose levels that are considered safe and desirable in other patients might be undesirable in diabetic patients with chronic hyperglycemia, and rapid and substantial lowering of their blood glucose levels during their acute illness/surgery may worsen clinical outcome [4]. Moderate glucose control for higher glucose target levels was recommended by the recent Surviving Sepsis Campaign guidelines in septic patients with high quality of evidence on this recommendation (GRADE 1 A). This recommendation is based on the results of randomized controlled trials (RCTs) [5-9] and meta-analyses [10-14] of intensive insulin therapy which had been performed during the last years. The RCTs studied mixed populations of surgical and medical ICU patients [5-9] and found that intensive insulin therapy did not significantly decrease mortality. All studies reported a much higher incidence of severe hypoglycemia (glucose ≤40 mg/dl) (6-29%) with intensive insulin therapy. Several meta-analyses also confirmed that intensive insulin therapy was not associated with a mortality benefit in surgical, medical, or mixed ICU patients [10-14].

Recent guidelines on nutritional support in burn patients reflect this trend and target higher levels of glucose than were previously recommended [15]. Also the exact cut off for beneficial glucose levels has not yet been defined in burn patients, these guidelines recommend that clinicians follow general ICU recommendations of glucose targets between 100 and 150 mg/dl. Observed benefits are shown in both retrospective and prospective studies in burn patients and include better graft take, fewer infectious complications, and decreased mortality rate [16-20].

1.2. Nutritional support

Critical illness is hallmarked by a severe catabolic response leading to energy and protein deficiency and skeletal muscle wasting. Many nutritional interventions are implemented during the acute phase of critical illness in an attempt to reverse this potentially harmful energy and protein deficiency. Whether it is beneficial to give highly targeted nutritional support early during critical illness in an attempt to reverse this catabolic response remains to be answered. Current evidence does not show benefits in trying to interfere with catabolic response in the early phase of critical illness. Moreover, the inability to tolerate sufficient nutritional support via enteral route early after disease onset is considered to be a part of the acute physiologic response to severe illness. The recent review article of Casaer, and Van den Berghe, on nutrition in the acute phase of critical illness [21] emphasizes that enteral nutrition intolerance may indicate how ill the patient is, may be a marker of the severity of illness (i.e., patients who can be fed enterally are less ill than those who cannot) rather than a mediator of complications and poor outcomes.

Uncertainty exists about the most effective route for delivery of early nutritional support in critically ill patients. Studies in animals and humans have shown a trophic effect of enteral nutrients on the integrity of the gut mucosa, and a lower risk of infection. These findings provided the rationale for instituting enteral nutrition early during critical illness in older publications [22-24]. However, the most effective route for early nutritional support in critically ill patients has continued to be discussed in the recent literature [25-27]. A recent CALORIES trial, evaluated the hypothesis that the parenteral route is not inferior to the enteral route for the delivery of early nutritional support in adult patients admitted to 33 Intensive Care Units in England [28]. Patients who could be fed through either the parenteral or the enteral route were randomly assigned to a delivery route, with nutritional support initiated within 36 h after admission and continued for up to 5 days. There were significant reductions in the parenteral group, as compared with the enteral group, in rates of hypoglycemia (P = 0.006) and vomiting (P < 0.001). However, there were no significant differences between the parenteral group and the enteral group in the mean number of treated infectious complications (0.22 vs. 0.21; P = 0.72), in 30-day and 90-day mortality rates, and in rates of other secondary outcomes, or adverse events. By 30 days, 393 of 1188 patients (33.1%) in the parenteral group and 409 of 1195 patients (34.2%) in the enteral group had died. Caloric intake was similar in the two groups, and the target intake not achieved in most patients. The authors of this study concluded that the early nutritional support through the parenteral route is neither more harmful nor more beneficial than such support through the enteral route.
Parenteral nutrition is not commonly used in burn centers due to concerns that it will lead to hyperglycemia, infection, and increased mortality. However, most of trials comparing enteral and parenteral routes of feeding were conducted in an era in which researchers may have underestimated the harm of pronounced hyperglycemia and overfeeding in critically ill patients, so the inadequate control of these situations may have led to biased results [21]. A recent retrospective study of Dylewski et al evaluated the efficacy of parenteral nutrition in pediatric patients admitted with burns ≥30% of total body surface area [29]. Of the 105 patients who met the inclusion criteria, 96 (91%) received parenteral nutrition or a combination of parenteral nutrition and enteral nutrition during their care and nine patients received only enteral nutrition. Protein intake was significantly higher in the parenteral nutrition group. Incidence of catheter-related blood infections or respiratory infections did not differ between investigation groups. The authors concluded that judicious use of hypocaloric, high-nitrogen parenteral nutrition is a safe and effective method of nutritional support in pediatric burn patients when nutritional targets cannot be achieved using only the enteral route.

1.2. Energy utilisation in critically ill patients has also been debated recently. The main shortcomings to calorie estimation in critically ill patients seem to be based on the following: 1. energy delivery are often estimated by using the patients’ characteristics before the onset of illness 2. energy use differs per patient and per day in the ICU and thus should be individually estimated on a daily basis preferably with the use of indirect calorimetry [21]. The findings of the recent EPaNIC and EDEN trials raise concern that highly targeted feeding early in critical illness does not provide benefits and may cause harm in some populations or settings [25, 30]. Implementation of the protocol resulted in earlier initiation of feeding and an increased attainment of caloric goals did not provide any benefit in terms of either mortality or length of stay in the ICU or hospital [31]. In the study of Arabi et al. [32] patients who were assigned to the approach that allowed underfeeding received fewer calories but had outcomes that were at least as good as those in patients assigned to early full feeding.

Advances in burn care have reduced the magnitude of the hypermetabolic response, resulting in more moderate feeding targets than were previously recommended. It is important to remember that the energy utilisation increase is most pronounced during the first weeks postburn and decreases progressively thereafter; the administration of too many calories has also been associated with increased rate of complications in critically ill burn patients. Interestingly, none of the methods used in burn patients over the last fifteen years correlate precisely with measured energy expenditure; most of them over-predicted energy expenditure [33]. Indirect calorimetry is considered to be the gold standard to determine energy consumption; however, this tool doesn’t exist in many burn units and is often technically difficult to perform. In absence of this tool the Toronto equation seems to be a well validated alternative to the traditionally used formulas [15]. The main difference from other methods is that the Toronto formula takes into consideration the changes of energy utilisation over time. However, the recently published recommendations on nutritional support of burn patients do not show a strong consensus of burn specialists and nutritionists on the use of this formula and the quality of evidence for this recommendation is quite low [15], so further research concerning this specific field is warranted.

1.2.2. Micro and micronutrients supply

It does not appear to be desirable to interfere with the early catabolic response to critical illness, either with macro and micronutrients or with hormones [21, 34, 35]. Two recent randomized controlled trials on the use of glutamine and anti-inflammatory lipids in critically ill patients, the REDOX and OMEGA studies [36, 37], were designed with the following simple physiological rationale: (1) omega-3 fatty acids contained in fish oils have shown efficacy in the treatment of chronic and acute inflammatory diseases due to their pleiotropic effects on inflammatory cell signaling pathways. In a variety of experimental and clinical studies, omega-3 fatty acids attenuated hyperinflammatory conditions and induced faster recovery; (2) glutamine is the most abundant nonessential free amino acid. It is synthesized predominantly in skeletal muscle; low glutamine levels have been associated with a poor outcome in critical illness. Low glutamine levels were considered to be the consequence of muscle wasting, since with the loss of muscle mass, the production of glutamine may not match increased glutamine use in immune cells, enterocytes, and hepatocytes. Thus, glutamine was labeled a “conditionally essential” amino acid during critical illness, which led to the hypothesis that glutamine supplementation would improve outcomes.

The effects of fish oil in infection rates and outcome were not found to be statistically significant in ICU patients, and dose-effect relationships were not established for any cohort [38]. The aforementioned OMEGA study [37] was stopped prematurely for futility when it showed no benefits with the administration of ω-3 fatty acids plus antioxidant supplements in 272 patients with acute lung injury. Currently, the lack of high-quality evidence precludes any recommendation on the use of specific lipids in critically ill patients [21].

In two recent high quality, randomized, controlled trials, investigators studied the effects of two doses of glutamine in critically ill patients. In the Scottish Intensive Care Glutamine or Selenium Evaluative Trial (SIGNET) [39], involving 500 patients, investigators evaluated the effects of a glutamine dose of 0.1 to 0.2 g per kilogram per day, whereas in the REDOX trial [36], investigators evaluated a glutamine dose of 0.6 to 0.8 g per kilogram per day. The SIGNET trial showed no benefits of low-dose glutamine administered parenterally to patients receiving parenteral feeding. The REDOX trial showed an absolute increase of 6.5 percentage points in the rate of death among patients with organ failure who received early high-dose parenteral nutrition plus enteral glutamine treatment. The recent post hoc analysis of the REDOX trial data was aimed to reevaluate the effect of glutamine and antioxidant supplementation after controlling for baseline covariates [40]. In total, 1223 mechanically ventilated adult patients with multiorgan failure were randomized to receive glutamine, antioxidants, both glutamine and antioxidants, or a placebo.
administered separately from artificial nutrition. After adjustment for baseline covariates, early provision of high-dose glutamine administered separately from artificial nutrition was not beneficial and may be associated with increased mortality in critically ill patients with multiorgan failure. For both glutamine and antioxidants, the greatest potential for harm was observed in patients with renal dysfunction upon study enrollment. All these examples illustrate the need for reevaluation of the simplistic physiological rationale, namely that substitution of specific nutrients and the restoration of their normal levels correlates with disease resolution. These examples illustrate the need for proof of the actual outcome benefits of macro and micronutrients supplementation.

A few small monocentric studies about glutamine supplementation in burn patients have been performed but present many variations in terms of dose, route and duration of administration, studied population or objectives [41–45]. Inconstant results are observed regarding the impact of glutamine supplementation on infectious complications, length of stay and mortality. The recent guidelines on nutritional support in burn patients mentioned that it is difficult to recommend a precise dose, a route, or duration of administration of glutamine in burn patients currently [35]. Although these guidelines suggest supplementation of glutamine, the consensus of burn specialists upon this suggestion is weak and the quality of evidence for these recommendations is also quite low.

2. ... but less is sometimes more

2.1. Hemodynamic monitoring

Treatment based on physiological monitoring, has been a cornerstone of teaching in critical care medicine for decades. Disease severity has been believed to be an important indicator of outcome, and the assessment of severity has been largely based on the degree to which the measured variables (e.g., perturbations of the cardiovascular, respiratory, and acid-base systems) differ from normal values. Established data have documented a close association between the sequential changes in physiological abnormalities and prognosis from acute illness [34,46]. In the same way that increasing deviation of variables from normal values reflects worsening of disease and poor prognosis, the converse is also true; normalization of abnormal variables parallels disease resolution and may be the principal objective evidence that a patient’s condition is improving, however, despite this rationale the approach may sometimes be imperfect [34]. As a vivid paradigm of this imperfect approach could be the inclusion of hypotension in diagnosis of shock. Several studies have actually shown that preserved blood pressure can be associated with markers of inadequate tissue perfusion, such as decreased central venous oxygen saturation (ScvO2) and significantly increased concentrations of blood lactate [47–49]. Conversely, persistent hypotension in patients with septic shock without increased lactate levels may have limited impact on mortality [50]. For these reasons, the definition of circulatory shock, emerging from the recent consensus on circulatory shock and hemodynamic monitoring created by the task force of the European Society of Intensive Care Medicine, does not necessarily require the presence of hypotension [51]. Rather, the consensus noted that the definition of shock as “life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells’ usually includes, but is not limited to, the presence of hypotension”. Regarding targets for blood pressure in the management of shock this consensus guidelines recommend the individualization of blood pressure for all patients. Consensus emphasizes that the ultimate goal is to improve tissue perfusion—not to achieve any specific blood pressure or DO2 value, which could ultimately lead to harming the patient. Consensus recommends not targeting any ventricular filling pressure or volume (recommendation level—1; Quality of Evidence—moderate (B)). The authors emphasize that fluid resuscitation should be guided by more than one single hemodynamic variable, preferably by using dynamic over static variables to predict fluid responsiveness, when applicable (recommendation level—1; Quality of Evidence—moderate (B)).

It is well known that the use of urinary output and conventional vital signs to guide initial resuscitation of burn patients may lead to suboptimal resuscitation. On the other hand, the use of invasive hemodynamic monitoring targeted to specific values may also not achieve the desirable results. Previous publications have shown that transpulmonary thermodilution (TPTD) monitoring results in more aggressive therapeutic strategies and is associated with a significant increase in fluid administration, but it does not improve preload [52–54]. Arlati and colleagues [55] introduced the concept of permissive hypovolemia in burn patients. In a study which included 24 burn patients, the authors used a permissive hypovolemia protocol and reduced the volume given as low as possible by titrating the infusion rate to a minimum intrathoracic blood volume index (ITBV1) value that allowed for at least 2.2 l/min/m² of the cardiac index (CI). The use of the protocol has been shown to be effective in reducing organ dysfunction. Sánchez and colleagues analyzed the performance of a permissive hypovolemia protocol guided by invasive hemodynamic parameters (transpulmonary thermodilution technique) and vital signs in a prospective cohort study on 132 burn patients over a 3-year period [56]. These patients underwent resuscitation guided by MAP (>65 mmHg), urinary output (0.5 to 1 ml/kg), transpulmonary thermodilution technique variables and lactate levels. An adequate cardiac index and tissue perfusion was achieved with below-normal levels of preload (Intrathoracic Blood Volume Index values less than 800 ml/m²). The authors concluded that early resuscitation guided by lactate levels and below-normal preload volume targets was safe and could avoid unnecessary fluid input. It seems that the way of estimating of hemodynamic status and resuscitation effectiveness in major burns is currently a controversial topic, but continuing developments and research may bring about a new approach to this important issue.

2.2. ARDS treatment

Different specific options were evaluated in the recent meta-analysis on therapeutic approach in ARDS patients [57]. The authors of this meta-analysis aimed to review all published randomized controlled trials (RCTs) on ARDS. In an umbrella
review of the evidence, they analyzed the results of RCTs on treatment of ARDS. The authors aimed to evaluate whether any interventions have robust evidence of curtailing mortality for this syndrome. Finally, they identified 159 published RCTs and 29 meta-analyses. A statistically significant survival benefit was observed in eight trials (seven interventions) and two trials reported an adverse effect on survival. Among RCTs two showed a statistically significant mortality benefit of the intervention (the use of lower tidal volumes and prone positioning), one showed a statistically significant mortality benefit only in adjusted analyses (the use of cisatracurium), and one (in use of high-frequency oscillatory ventilation) showed a significant detrimental effect. Across 29 meta-analyses, the most consistent evidence was shown for low tidal volume and prone positioning in severe ARDS. The authors concluded that there is limited supporting evidence that specific interventions can decrease mortality in ARDS. While low tidal volumes and prone positioning in severe ARDS seem effective, most sporadic findings from other interventions suggesting reduced mortality are not corroborated consistently in large-scale studies including meta-analyses. Among other interventions, neuromuscular blockers have shown tentative benefits. Neuromuscular blockers may improve oxygenation and decrease inflammation [58,59]. Cisatracurium has shown a survival benefit when compared to placebo [60], but not in an unadjusted analysis. High levels of PEEP have also not conclusively shown an improved survival rate. This intervention might be beneficial in patients with severe ARDS, as in the case of prone ventilation, but this hypothesis needs to be validated in a large trial. The recent meta-analysis of Tonelli et al. [57] identifies two major factors which could explain the long list of negative RCTs in ARDS: first, excessive heterogeneity in study populations and second, a lack of standardization of outcome measures.

In their comments on this article Villar et al. [61] emphasize that after 25 years and hundreds of millions of euros/dollars of clinical research funding, only three specific interventions have been found which could decrease ARDS mortality: the use of low tidal volumes, prone positioning, and the use of neuromuscular blockers early in the course of severe ARDS. The authors sound the alarm that if researchers do not learn from the past, do not set new approaches, new standards for identifying subsets of ARDS patients with similar severity of illness, and standardizing clinically relevant outcomes, they will continue performing negative RCTs that should be burned after being read. Conversely, even though the meta-analysis of Tonelli et al. has given us more clarity than we have ever had before, it may also create the impression that patients with severe ARDS should be rendered bedbound, medicated with high doses of sedatives and neuromuscular blockers in order to facilitate a protective ventilation strategy [62]. Strategies to improve ventilation and oxygenation may lead to the development of right ventricular dysfunction and low cardiac output with hemodynamic support both by fluids and inotrops and increase the risk of acute kidney injury [63]. There is a need for a paradigm shift in our approach to the treatment of ARDS patients by using alternative means of gas exchange, such as extracorporeal respiratory support [62]. Both extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal (ECCO2R) have the potential to better address the heterogeneity in lung injury, which is central to VILI (Ventilatory Induced Lung Injury). On the other hand, these techniques are equally invasive, not widely available and have their own complications [64–67].

Only a small number of experimental and clinical trials, all with a limited number of patients, are available in studies of burn patients [65–70]. Large, high-quality, randomized, controlled trials supporting an outcome benefit by using ECMO and extracorporeal carbon dioxide removal in critically ill burn patients have not yet been performed; therefore further research on the use of these techniques is warranted.

In conclusion, the recent studies in the field of critical illness management have enriched our knowledge and forced us to revise our views on many points. These recent publications “shook the world of critical care” changing our conventional beliefs and stereotypes. The consequences of the “Ten Days That Shook the World” [71] hardly led to a better future. Violent historical turbulence damaged millions of lives and still continues to affect history. How the recent revolutionary publications which “shook the world of critical care” will lead to a better future for millions of our patients will soon be seen.

Conflict of interest statement

There is no any conflict of interest to declare.

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