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EDITORIAL

Focus on fluid therapy and nutritional support

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Recent studies have challenged several widely accepted concepts in fluid and nutritional management. A series of articles in *Intensive Care Medicine* reflect the ongoing debate and areas of uncertainty.

How much intravenous fluid should be administered to patients with sepsis and hypotension or hyperlactatemia? A fixed 30 mL/kg as recommended by the Surviving Sepsis Campaign guidelines [1, 2], or an individualized amount, perhaps 250–500 mL boluses followed by reassessments of the circulatory response? [3] There are no randomized trials comparing these two strategies [2]. The supporters of the fixed 30 mL/kg of fluid suggest that this would be sufficient to correct hypovolemia in most patients without harm [2]. The 30 mL/kg is not meant to negate an individualized assessment as some patients may need more fluids [2]. Observational data suggest that this strategy of fluid resuscitation is associated with reduced mortality [2]. In addition, using a protocol of a fixed minimum amount of fluids may facilitate wide implementation as assessment of fluid responsiveness may not occur in many clinical settings [2]. The opposite view suggests that such an approach ignores the complex circulatory failure in sepsis in which hypovolemia is combined with vasodilatation and myocardial depression [3]. In addition, there is increasing evidence for harm associated with excessive fluid administration [3]. Instead, a thorough clinical assessment and, in selected patients, more advanced hemodynamic monitoring will better identify those who will benefit from fluids, vasopressors, or inotropes [3]. The results of the FEAST (Fluid Expansion as Supportive Therapy) trial are often considered [3, 4]. The trial showed increased mortality with albumin or saline boluses compared to no fluid boluses [4]. However, FEAST was conducted in African children, many of whom had malaria and severe anemia with no or minimal access to mechanical ventilation [2]. Therefore, the results of FEAST may not be generalizable to adult patients with sepsis [2].

In addition to the debate regarding the amount of resuscitation fluid, the clinical benefit of hydroxyethyl starch (HES) has been an area for extensive debate. In 2013, the European Medicines Agency published a decision of the European Commission that HES solutions must no longer be used to treat patients with sepsis or burns or critically ill patients because of an increased risk of kidney injury and mortality, although HES would be available in other selected indications [5–8]. Since then the consumption of HES has declined not only in ICUs but also in anesthesia and emergency departments [9]. But is the controversy over? Three articles in *Intensive Care Medicine* in 2017 addressed different aspects of this debate [8–10]. Evidence for harm includes data demonstrating increased risk of acute kidney injury with HES in surgical and non-surgical ICU patients, and in patients with sepsis [10]. In addition, HES has been associated with an increased risk of bleeding in patients with sepsis and those undergoing major surgery [10]. Most concerning are the data from meta-analyses in critically ill patients demonstrating increased mortality with HES [10]. However, the issue may be more complex [11]. It has been suggested that trials of HES therapy were of heterogeneous design [11]. Some of these studies had delayed enrollment of patients and used HES not only in the early phase of resuscitation [11]. The indications for fluid resuscitation may not have been standardized and the amount may have been above the recommended dose [11]. In contrast, the CRISTAL trial that compared any

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crystalloid to any colloid in ICU patients with hypotension, hypovolemia, and tissue hypoperfusion found no difference in the primary endpoint 28-day mortality or need for renal replacement therapy (RRT) [11, 12]. There were differences in secondary endpoints favoring colloids, including shorter duration mechanical ventilation and cardiovascular support and lower 90-day survival [12]. However, the trial had a higher risk of bias [13], adding to the HES controversy [9, 14, 15].

In addition to the debates regarding intravenous fluids, recent papers reflected the uncertainties regarding nutritional support in critically ill patients. The 2017 European Society of Intensive Care Medicine (ESICM) clinical practice guidelines for early enteral nutrition (EN started within 48 h) included 17 recommendations supporting early EN and seven recommendations supporting delayed EN [16]. The guidelines suggested delaying EN in critically ill patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate in excess of 500 mL/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access [16]. All recommendations were graded as weak because of the low quality of evidence, with several based only on expert opinion [16].

Along this line, an expert panel outlined a roadmap for research agenda in nutrition and metabolism [17]. Recent randomized trials have challenged several concepts, including the notion that energy expenditure must be met universally in all critically ill patients during the acute phase of critical illness by the use of EN or parenteral nutrition (PN) [17]. Current literature leaves uncertainties in nutritional support including energy expenditure and monitoring of nutritional effects across patients with different nutritional risks, substrate requirements, the interrelationship between nutrition and functional recovery, management of intestinal and gastric feeding intolerance, and immune-modulating nutrition [17]. The panel prioritized the top 10 studies for the coming next 10 years. The optimal protein dose combined with mobilization during the acute phase and post-acute phase of critical illness was considered a high research priority [17].

Another aspect related to the gastrointestinal function in critically ill patients, stress ulcer prophylaxis (SUP) with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists, has been questioned lately [18]. SUP is recommended in ICU patients at risk for gastrointestinal bleeding and has become a measure of quality of care. However, there is increasing evidence to suggest that PPIs are associated with increased risk of nosocomial pneumonia and *Clostridium difficile* infections [18]. Two randomized trials are comparing PPI to placebo in adult ICU patients. The SUP-ICU (Stress Ulcer Prophylaxis in the Intensive Care Unit) trial has been completed and showed that mortality at 90 days and the number of clinically important events were similar in those assigned to pantoprazole and those assigned to placebo [19, 20]. The REVISE (Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding in ICU) trial has completed a feasibility stage but the main trial has not started [21]. The PEPTIC (Proton pump inhibitors vs. histamine-2 rEceptor blockers for ulcer Prophylaxis Therapy in the Intensive Care unit) trial is a cluster-randomized crossover trial comparing PPI to histamine-2 receptor antagonists [18].

Recent clinical trials have resulted in major advances in fluid therapy and nutritional support in critically ill patients. The future focus will continue to be addressing high priority research questions by well-designed and adequately powered clinical trials.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no competing interests.

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