Gluttony in the Intensive Care Unit

Time to Push Back from the Consensus Table

Numerous consensus statements have endorsed early and full nutrition in critically ill patients, with one recommending parenteral supplementation in patients unable to tolerate full enteral nutrition (1–3). However, the EPaNIC study demonstrated that critically ill patients who had their enteral nutrition supplemented with parenteral nutrition during their first week in the intensive care unit (ICU) had worse outcomes than those who received only whatever enteral nutrition they could tolerate (4). Similarly, the ARDS Network EDEN trial failed to demonstrate benefit from increased enteral caloric intake above trophic level enteral feedings early in the ICU stay (5). The results of these trials cast doubt on the previous dogma that full nutritional support should be provided as early as possible to critically ill patients, and that administering more calories improves outcomes. Two common questions surrounding these trial results arose—namely whether or not full nutritional support was undertaken in the patients most likely to benefit from it and whether the nutrition contained the optimal ingredient proportions to help said patients.

One of the main criticisms of the EPaNIC study was that it enrolled a large number of critically ill patients, over half of whom were post–cardiac surgery, who were not at risk for malnutrition, or who were not sick enough to benefit from parenteral nutrition (6–9). Naysayers argued that the lack of benefit, or even potential harm from parenteral nutrition in these patients obscured any beneficial signal in the minority of critically ill patients who may have benefited. Unfortunately, identifying which critically ill patients are most likely to benefit from nutritional support remains hotly debated. In fact, although we assume that full nutrition improves outcomes in those who are already malnourished at ICU admission, there is no evidence to support this belief. Many surmise that those with higher severity of illness and thus, more likely to experience higher levels of catabolism, extended duration of critical illness, and more muscular atrophy are the patients most at risk for malnutrition, and therefore most likely to benefit from early initiation of full artificial nutrition.

A second major criticism of the EPaNIC study concerned the ingredients in the parenteral nutrition. The EPaNIC protocol started peripheral nutrition with calories from glucose with standard parenteral nutrition containing protein and lipids slowly added over time. This strategy resulted in insufficient protein to support critically ill patients, especially early in their ICU stay (7–9). Critics argue that protein is more important and that early glucose administration, especially in centers risking hypoglycemia by using insulin infusions to obtain tight glucose control (10), may have been detrimental to patients.

Although their study is not without limitations, Casaer and colleagues attempt to answer these two important questions in their article published in this issue of the *Journal* (pp. 247–255) (11). They use very complex statistical methods to undertake two distinct, but equally important, *post hoc* analyses of the 4,640 patients enrolled in the EPaNIC study. Similar to the overall study, time to alive discharge from the ICU represented the primary outcome. This endpoint avoids the bias from informative censoring of patients who die early in the ICU, as it assigns ICU deaths a longer length of stay than any survivor (12).

To examine the possibility that early parenteral nutrition may have differing effects on critically ill patients based on their severity of illness, Casaer and colleagues analyzed their results by APACHE II quartile. Unfortunately, these results failed to identify any quartile where early parenteral nutrition improved time alive in the ICU or development of new infection. However, severity of illness may not represent the best predictor of which critically ill patients are likely to benefit from early full artificial nutrition. Maybe the sickest patients are the ones least likely to survive long enough to experience the benefit, or have such high levels of inflammation and catabolism that they are unable to effectively use artificial nutrition. A separate analysis by Casaer and colleagues of only the medical and emergent surgical critically ill patients similarly failed to demonstrate benefit from early parenteral nutrition.

In an attempt to answer the criticism about calories and ingredients, Casaer and colleagues combined the early and late parenteral nutrition groups to look at outcomes by overall amount of calories received regardless of enteral or parenteral route (their Figure 2), percent of energy target received (their Figure E1), and amount of glucose and protein received (their Figure 3). To avoid time-dependent bias (i.e., patients who survive longer are likely to be exposed to more nutrition), clinical outcomes were compared for nutritional intakes up through five different time points (Days 3, 5, 7, 10, and 14). The analyses suggested an inverse relationship between overall caloric intake (regardless of route) and time to alive ICU discharge, meaning that the more calories patients received, the less likely they would survive to ICU discharge. A similar inverse relationship was suggested with the amount of protein received and time to alive ICU discharge, whereas glucose had a neutral effect.

Many will continue to argue that we still are not studying (or analyzing) the correct patient populations. Some will suggest we should aggressively pursue early full nutrition in critically ill patients who remain critically ill long enough for malnutrition to occur or those identified by admission nutrition risk assessments, such as the NUTRIC (13) or Nutritional Risk Screening (14) score. Unfortunately, it is not clear when malnutrition begins during critical illness, which probably varies by individual patient, and it is impossible to predict at the time of ICU admission which patients will survive, yet remain critically ill long enough to experience malnutrition. In addition, despite limiting enrollment to patients at high risk for malnutrition (as demonstrated by a score of 3 or greater on the Nutritional Risk Screening score [5]), the EPaNIC study still found that early parenteral nutrition resulted in worse clinical outcomes.

There does not seem to be a readily identifiable subset of patients for whom early parenteral nutrition is beneficial with regard to either time to discharge alive from the ICU or reduced infections. Furthermore, these data also suggest that both increased calories and total protein, regardless of route of administration, are associated with worse clinical outcomes. Due to the observational and *post hoc* nature of these analyses, cause and effect cannot be ascertained. Higher caloric intake may not directly cause worse time to discharge from the ICU alive, but merely be associated

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with it through other confounders. However, these data do help us better understand the effect of nutrition, and especially early parenteral nutrition, on critically ill patients. It does provide one explanation as to why patients given early parenteral nutrition in the EPaNIC study experienced worse outcomes. These data do not inform as to whether some nutrition is better than starvation, nor do they inform us how to treat patients who are already malnourished at ICU admission. Given the available data, it appears that in most critically ill patients, nutrition may be another treatment in the ICU where less is more.

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Extracorporeal Membrane Oxygenation Rescue for H1N1 Acute Respiratory Distress Syndrome

Equipoise Regained

In this issue of the *Journal*, Pham and colleagues (pp. 276–285) report patient outcomes after extracorporeal membrane oxygenation (ECMO) as a rescue therapy for acute respiratory distress syndrome (ARDS) during the 2009–2011 H1N1 influenza pandemic (1). Patients who received ECMO were compared with largely concurrent patients with H1N1 ARDS who did not have ECMO, by matching patient characteristics using propensity scoring. The pandemic timing did not permit a randomized controlled trial, but it provided a unique opportunity to study a substantial sample of patients receiving venovenous ECMO for ARDS in France from a single etiology. The REVA investigators are to be congratulated for building the impressive collaborative national network of clinician-investigators that enabled this research.

Four multicenter observational studies from different countries have been published after the 2009 H1N1 pandemic. These report a mortality rate varying from 14 to 41% (2–5) and varying rates of all rescue therapies used for severe hypoxemic respiratory failure. In particular, there were large differences in the rate of ECMO as a rescue therapy (0–39%) (2–5). Mortality rates after ECMO have previously been reported as 37% at 6 months (6), 32% at hospital discharge (3), and 29% at intensive care unit (ICU) discharge (2). Mortality at hospital discharge may be less when ECMO is initiated within the first 7 days of mechanical ventilation (3) and if the complications of ECMO could be reduced.

A prospective observational study from the United Kingdom (UK) (7) concerning the same pandemic had reported that referral to an ECMO specialist center improved patient outcomes. In France, Pham and colleagues found instead that there was no difference in patient outcomes after ECMO, and the mortality trend was toward harm (1). Both studies used propensity score (PS) matching and large observational cohorts from similarly large patient populations during the same H1N1 epidemic.

The REVA ECMO investigators (1) comprised 114 ICUs throughout France in hospitals of varying sizes and complexities, of which 30 used ECMO as optional rescue therapy for ARDS. Many, but not all, of the ECMO and control patients were managed concurrently in the same centers. In the UK cohort (7), patients were transferred to one of four ECMO specialist centers, whereas the controls were managed without transfer at many different, less specialized ICUs.

PS matching is an imperfect art, with several methodological variations. Unlike conventional adjustment using an overall index of severity (e.g., APACHE score), PS matching in both studies used a number of individual patient covariates to construct a model to match control patients. The specific matching method chosen by Pham and colleagues (1) (1:1 match, without replacement) uses each control patient only once. This avoids a potential source of error (inherent when a control is replaced back in