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Immunonutrition in critical illness: still fishing for the truth

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Expanded Abstract

Citation

Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. *Intensive Care Med* 2008;34:1980-1990 [1].

Background

The role of immuno-modulating diets (IMD's) in critically ill patients is controversial.

Methods

Objective: The goal of this meta-analysis was to determine the impact of IMD's on hospital mortality, nosocomial infections and length of stay (LOS) in critically ill patients. Outcome was stratified according to type of IMD and patient setting.

Data Sources: MEDLINE, Embase, Cochrane Register of Controlled Trials.

Study Selection: RCT's that compared the outcome of critically ill patients randomized to an IMD or a control diet.

Data Synthesis: Twenty-four studies (with a total of 3013 patients) were included in the meta-analysis; 12 studies included ICU patients, 5 burn patients and 7 trauma patients. Four of the studies used formulas supplemented with arginine, two with arginine and glutamine, nine with arginine and fish oil (FO), two with arginine, glutamine and FO, six with glutamine alone and three studies used a formula supplemented with FO alone. Overall IMD's had no effect on mortality or LOS, but reduced the number of infections (OR 0.63; 95% CI 0.47-0.86, P = 0.004, I^2 = 49%). Mortality, infections and LOS were significantly lower only in the ICU patients receiving the FO IMD (OR 0.42, 95% CI 0.26-0.68; OR 0.45, 95% CI 0.25-0.79 and WMD -6.28 days, 95% CI -9.92 to -2.64, respectively).

Conclusions

An IMD supplemented with FO improved the outcome of medical ICU patients (with SIRS/sepsis/ARDS). IMD's supplemented with arginine with/without additional glutamine or FO do not appear to offer an advantage over standard enteral formulas in ICU, trauma and burn patients.

Commentary

The widespread recognition that critical illness is characterized as a state of immunosuppression and inflammation has lead to the development of nutritional support products or interventions designed to enhance the host immune response and/or suppress inflammation. Importantly, the use of immune modulating diets (IMD) in critically ill patients needs to be translated into improvements in clinically relevant outcomes such as infectious morbidity, mortality and length of stay. While IMD's containing immunonutrients such as glutamine, arginine, and omega-3 fatty acids are conceptually appealing, data from multiple individual trials and several meta-analyses have failed to produce convincing evidence that important clinical outcomes are favorably affected in critically ill patients [2]. Prior quantitative reviews of immunonutrition have been confounded by grouping different immune enhancing formulas and different types of patients together, introducing heterogeneity and perhaps masking treatment effects [3-7].

In the current study, Marik and Zaloga [1] performed a meta-analysis of published randomized controlled trials of IMD's in critically ill patients to test the hypothesis that effects of IMD's might be apparent if the analysis accounted for the type of IMD formulation used and the subgroup of critically ill patients in which the IMD's were employed. Their

search strategy yielded a total of 24 randomized controlled trials with 12 of these studies identified as occurring in an ICU setting, 5 studies performed in burn patients and 7 studies performed in trauma patients. Commercially available immune enhancing enteral diets were employed in these studies and for the purposes of analysis, were categorized by the investigators as containing arginine alone; arginine and glutamine; arginine and fish oil (FO); arginine, glutamine and FO; glutamine alone; and FO alone. The clinical outcomes of hospital mortality (N = 23 studies), new infections (N = 21 studies) and hospital length of stay (LOS) (N = 13) were analyzed. When available, the outcomes were assessed on an intention to treat basis.

The combined analysis revealed no effect of IMD's on mortality or LOS. However, IMD's were favored in reducing new infections. Subgroup analysis by type of IMD revealed that only the ICU subgroup receiving FO alone (N = 3 studies) had significant effects on all study outcomes (mortality, secondary infections and LOS). Subgroup analysis by patient category revealed a reduction in secondary infections and LOS in ICU patients that was not apparent if the analysis excluded patients who received FO alone. Effects in other subgroups by IMD or patient group were not evident. The authors concluded that FO IMD's improved outcomes in medical ICU patients with SIRS, sepsis, or ARDS.

While the authors recognized some of the inherent weaknesses in their meta-analysis including the small numbers of studies for subgroups based on type of IMD, an explicit analysis of the quality of the studies included in the review would have been helpful. The authors' main findings were based on the results of three clinical trials, each with methodological limitations. In the first study, the effect of an enteral diet consisting of FO and antioxidant vitamins in patients with ARDS was evaluated in a randomized double-blind multi-center study [8]. This study was not powered to detect differences in mortality, nor was it specifically designed to evaluate new infections. In the intention to treat analysis, there was no difference in hospital mortality, hospital length of stay, or the development of infectious complications. The second study [9] was a double-blind single-center study of the same FO and antioxidant vitamin supplemented enteral diet in patients with severe sepsis or septic shock with a primary outcome of all cause 28-day mortality. While a difference in 28-day mortality was suggested by the data, an intension to treat analysis was not performed and infectious morbidity and hospital length of stay were not reported. The third study [10] evaluated the same enteral formulation in a single-center study of patients with acute lung injury. This study was not blinded and evaluated oxygenation and respiratory compliance as primary outcomes. In this study, there was no difference in hospital length of stay or survival and infectious morbidities were not reported. Given the variability in study design, methods, patient populations, and outcome variables tested, the conclusions drawn from the combination of these three studies should be carefully weighed.

These results highlight the complexities of immunonutrition in critically ill patients and lend further support to an emerging paradigm shift from immunonutrition to pharmaconutrition, where specific nutrients are evaluated independent of providing calories and protein to the patient [4]. The data from this review and the others preceding it leave us hopeful that it may be the last meta-analysis of immunonutrition using commercially produced products containing multiple potential immunonutrients. As suggested by Jones and Heyland [2], future studies should be designed similar to drug trials. That is to say that the effect of individual immunonutrients should be assessed independent of standard nutritional support and clinically relevant outcomes evaluated in well-defined populations of critically ill patients.

Recommendation

In summary, while this meta-analysis suggests a potentially beneficial effect of fish oil based IMD's in a subset of critically patients with SIRS, sepsis, or ARDS, the data upon which these conclusions are drawn are too weak to endorse a strong recommendation for use in these populations. The question of whether fish oil or any other potentially immune-modulating nutrient has real and measurable value in critically ill patients will depend largely on data drawn from well-designed and adequately powered trials based on the emerging concept of pharmaconutrition.

Competing interests

The authors declare no competing interests.

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