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EDITORIAL

C-reactive protein in immunometabolism: spared from 'paying the piper'

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Malnutrition and inflammation have a brutal bidirectional relationship. Malnourished individuals who become critically ill have heightened inflammation and worse outcomes compared to well-nourished counterparts [1]. Conversely, inflammation promotes muscle wasting, which impairs quality of life in critical illness survivors [2]. Thus, macronutrient delivery remains pivotal for thwarting the unintended maladies of critical illness. Even though the optimal timing and dose of nutrition during the acute phase of critical illness are unknown, clinical nutrition societies worldwide endorse enteral macronutrient delivery [3, 4]. Less is known about the role, timing, and dose of parenteral nutrition (PN).

The EPANIC trial randomized 4640 critically ill patients to early PN (day 3) or late PN (day 8) [5]. More than 80% enrolled were surgical patients and > 60% cardiac surgery. Those receiving early PN received a 20% glucose solution through day 2 and the late PN group received 5% glucose infusion and EN throughout. As compared to the early PN group, the late PN group had (1) an increased likelihood of being discharged earlier from both the intensive care unit (ICU) and hospital and without a difference in functional disability, (2) fewer infections, (3) less days of mechanical ventilation, and (4) lower duration of renal-replacement therapy [5].

Post-hoc analyses demonstrated the early PN group, as compared to late PN, had impaired markers of autophagy, more aminoacid catabolism, and the quantity of both calories and protein delivered were independently associated with worse clinical outcomes [6–9]. These data offer hypothesis-generating mechanisms for adverse clinical outcomes with early PN.

Despite the observed differences favoring late PN, a higher median C-reactive peptide (CRP) during the ICU stay was paradoxically higher in the late PN group [190.6 mg/l (100.8–263.2)], compared to the early PN group [159.7 mg/l (84.3–243.5)] [5]. In this issue of *Intensive Care Medicine*, Ingels et al. [10] conducted a secondary analysis of EPANIC to investigate whether the elevated CRP in the late PN group was related to cytokines from systemic inflammation or timing and/or dose of PN in patients who stayed in the ICU for at least 3 days. They hypothesized the rise in CRP in the late PN group, caused by systemic inflammation, was protective against new infections.

At day 3, CRP peak was higher in the late PN group compared to early PN [216 mg/l (152–274) vs. 181 mg/l (122–239), p-value < 0.0001]. During the first 3 days, the late PN group, as compared to early PN, had received less calories from protein and carbohydrates and needed less insulin to control blood-glucose level, yet both groups had similar baseline and day 3 levels of interleukin-6 (IL-6), IL-10, and tumor necrosis factor-alpha (TNF-α). The late PN group had fewer new infections after ICU day 3, as compared to early PN (24.4% vs. 31.3%, $p = 0.0008$). Furthermore, a higher change in CRP from baseline to day 3 was independently associated with a higher risk for new infection [adjusted odds ratio (aOR) 1.018 (1.006–1.03) per every 10 mg/l increase in CRP]. The authors conclude lower carbohydrate and protein intake in the late PN group were independently associated with a higher CRP level. However, using a mediation analysis, they were unable to demonstrate that the nutritional intervention was directly linked to the CRP rise, nor were the effects of the intervention on infection rates mediated by CRP. Appropriately, the authors highlight the inherent

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inability of the mediation analysis to allow for known and unknown confounders.

How do we reconcile the paradox of observing a higher CRP level, during the first 3 days of critical illness, being associated with improved clinical outcomes in patients receiving late PN, as compared to early PN?

An acute phase protein, CRP was discovered in 1930, and named for its reaction with the capsular polysaccharide of *Pneumococcus* [11]. CRP transcription occurs within 24–72 in multiple tissues in response to pro-inflammatory cytokines [12]. CRP is also an immune mediator via complement activation. Baseline level variation results from multiple metabolic factors, however, 50% of variance is associated with the number of dinucleotide repeats in an intronic region of the human CRP gene [13]. While widely used as a marker of inflammation, CRP cannot identify the type of inflammation (pro- or anti-) nor mobilized inflammatory cell function. CRP consists of several isoforms that bind to different receptors and therefore display distinct functional properties [14].

Based on the pleomorphic underpinnings elevating CRP, we offer an adjudication. The authors hypothesized the rise in CRP appeared to have a beneficial effect on reducing infectious complications in the late PN group by activation of complement-mediated clearance of organisms and preservation of autophagy, which enhances innate and adaptive immunity to degrade intracellular pathogens and prevent excessive inflammation. Unfortunately, these theories are not supported by a parallel reduction in static measurements of pro-inflammatory cytokines (IL-6 and TNF-α) nor a rise in the anti-inflammatory cytokine IL-10. Instead, cytokine levels were similar in both early and late PN groups. We agree that CRP is, at best, a non-specific marker of cytokine-induced inflammation and complement-mediated anti-inflammation. However, without comprehensive pro- and anti-inflammatory mediator profiling, any conclusion linking CRP to a clinical outcome must be tempered with confounding by indication, whereby unmeasured confounders may have a heavy hand in explaining the observed findings.

Overall, the results must be interpreted with caution. Immune modulating diets have failed to produce convincing evidence of their beneficial effect in critically ill patients by grouping different formulas and different types of patients together. Selecting patients based on their plasma CRP values could represent an interesting criterion, though these data suggest CRP may be a biomarker (associated) as opposed to a biologic signature (causally associated) of immunomodulation.

The authors should be congratulated for their hypothesis-generating work in linking a biologic marker to a clinical outcome. In general, surrogate markers should be biologically linked to a patient-centered outcome. In critical care nutrition trials, surrogate outcomes have often failed to biologically link to clinical outcomes [15]. When clinicians utilize unproven surrogate outcomes to titrate therapies, patients must bear the consequences ('pay the piper'). Fortunately, the non-specific CRP unbinds clinicians from using it to titrate nutrition dose and their patients are spared from 'paying the piper'.

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Declarations

Conflicts of interest
ZP, JJP, and J-MT have no conflicts of interest to disclose.

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