Response to Igor Eckert: Sometimes, the absence of evidence is evidence of its absence

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“The absence of evidence is not evidence of absence”, is an aphorism attributed to Carl Sagan [1], which is invoked when claims of the existence of God are encountered. Nonetheless, it is a succinct and elegant statement, which in this instance is simultaneously beautiful and wrong. At first glance, the lack of evidence is not evidence of absence, would suggest that for every treatment: medical, nutritional, or alternative therapy unless science has exhausted every mechanistic process available we cannot state it does not work even after randomised, double-blind studies, or as is the case here, multiple systematic reviews, none of which have found mortality benefit.

However, our recent study [2], that Dr. Eckert has shown interest in and has commented on, does not fit into this logical argument. Immune modulating nutrition has been studied for over 30 years now, in medicine, surgery and in critical care. We have over the years gained better understanding of how it works, and perhaps when best to administer it. Over the years, several studies have been performed on immune modulating nutrition and several meta-analyses have been generated from these. The utility of the latter is in allowing us to pool data from several studies to answer questions when perhaps individual studies might not have had power to do so. Our own recent meta-analysis on 1387 patients [3] showed that immune modulating nutrition given at least 5-days, but preferably 7-days, prior to surgery for gastrointestinal cancer was beneficial in reducing infective complications but not mortality. Similarly, Probst et al. [4] studied the use of immune modulating nutrition in 83 RCTs that included 7116 participants and found no survival benefit. All of these studies, however, were reporting short-term mortality.

As detailed in our paper [2], there are now studies which suggest potential long-term survival benefit, which prompted the assessment of long-term survival in our cohort,

showing no benefit. We agree that the confidence intervals are wide, but as described by Sackett et al. [5], to improve the precision around this estimate, would require a quadrupling of the study participants.

$$Confidence = \frac{Signal}{Noise} \times \sqrt{Sample\ size}$$

The noise (or uncertainty) in an RCT is the sum of all the factors ("sources of variation") that can affect the absolute risk reduction or absolute difference. In this case, compliance with the intervention, the exact tumour type, additional therapies that patients might have had such as neoadjuvant and adjuvant therapy might have all influenced the noise. As our study [2] was a follow-up of a previous study [6], it was both impossible and impractical to quadruple the sample size at this stage, to improve the precision of the estimate.

Therefore, if we cannot employ an increase in the sample size to reduce the signal-to-noise ratio, we have to rely on biological plausibility. Immune modulating nutrition, given for 10-15 days postoperatively is always going to be hard to justify as a mechanism of improving long-term survival in patients with gastrointestinal cancer, and we would suggest that this should not be the intention of using immune modulating nutrition. That is not to say, we do not think it could improve survival. Infectious complications after gastrointestinal cancer surgery can cause delays to chemotherapy, radiotherapy and other adjuvant treatments which might have improved overall survival. In critical care, Bear et al [7] suggest that mortality should not be used as the primary indicator in nutrition trials. They state: "the biological plausibility that small alterations in protein/energy delivery or changes in the timing or mode of nutrition delivery will result in detectable changes in mortality is low." They continue, "Our patients are subjected to many other potential threats to mortality,

independent of nutrition. For this reason, discussions around more appropriate outcomes to measure..” need to be had.

Finally, Dr. Eckert also incorrectly interpreted our conclusions. They read as follows [2]:

> “Despite, and perhaps because of all these possible shortcomings of our study and those of others, there is currently very little evidence upon which to base a recommendation that, in patients undergoing major surgery for cancer, feeds containing extra immune modulating nutrients have any benefit in terms of mortality, either in the short-term or long-term, over standard feeds aimed at treating or preventing malnutrition and its consequences.”

In this conclusion, we do not argue against immune modulating nutrition in the perioperative setting. However, based on biological plausibility, evidence from meta-analyses, and our findings of no mortality difference (with complete follow-up), we feel that we do not have any evidence at this point to justify the use of immune modulating nutrition solely for long-term survival benefit. Indeed, if any benefit existed (which could not be demonstrated in studies that have pooled data from over 7000 patients), then it would be so negligible as to not be clinically relevant.

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