Response to Knight SR, *et al.*: The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer

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Author Contributions:

All authors contributed equally to this letter.

To the Editor,

We thank Knight and colleagues[1] for their interest in our recent meta-analysis on immune modulating nutrition (IMN) in patients undergoing surgery for gastrointestinal cancer.[2] While we appreciate their comments, we would like to clarify our methodology and interpretation.

We included all participants in randomized clinical trials (RCTs) undergoing surgery for gastrointestinal cancer and receiving preoperative IMN for at least 3-days preoperatively. Hence, there were participants with and without malnutrition. However, as malnutrition may be present to a varying degree in at least 40% of patients undergoing cancer surgery, this mixed population of well-nourished and malnourished participants in the meta-analysis is representative of what would be observed in everyday clinical practice. Although the reduction in infective complications and length of stay was greatest in the study that included only malnourished participants,[3] this benefit was still present in some studies that included less than 10% of malnourished participants.[4-6] We, therefore, hypothesize that whilst IMN is beneficial in reducing infective complications in all patients undergoing surgery for gastrointestinal cancer, it is potentially more beneficial to those who are malnourished. Hence, we disagree with the assertion that this mixed population of participants, who met the inclusion criteria of each of the individual studies, were a “highly selected patient group”.[1]

Not all the individual studies had defined their infective complications using established tools such as the Centre for Disease Control and Prevention guidelines[7] or the Veterans Administration definitions.[8] Additionally, not all studies had defined what regimens were used for perioperative antibiotic prophylaxis or antiseptic preparation. We, therefore, had

to assume that in each individual study, patients in the intervention and control arms would have been treated similarly. We also had to accept the possibility of clinical and statistical heterogeneity due to the potential variability in practices. Infective complications in each individual study did not only refer to surgical site infections as interpreted by Knight and colleagues.[1] Infective complications included surgical site infections, deep wound infections, chest infections, intra-abdominal infections and urinary tract infections – all of which are possible complications that can occur after major surgery for gastrointestinal cancer. However, to account for the possibility of clinical and statistical heterogeneity between studies, we adopted the random effects model and for this particular outcome found heterogeneity to be low.

We limited our searches to the Embase, Medline and Cochrane databases, and also undertook hand searches of the bibliographies of the studies that met the inclusion criteria. No studies were identified from low and middle income countries (LMIC) specifically. Following the comment from Knight and colleagues,[1] we have searched the World Health Organisation Global Index Medicus database and have found no additional studies from LMIC evaluating the preoperative use of IMN in patients undergoing surgery for gastrointestinal cancer. We have also explored other published systematic reviews that have evaluated this question in other settings and in other surgical specialties and have not been able to identify any study from LMIC. There is clearly an information gap with regards to data on preoperative IMN in in patients undergoing surgery for gastrointestinal surgery in LMIC and teams with expertise in Global Surgery may wish to bridge this gap.

Whilst the impact of IMN on patients with malnutrition and advanced cancer might be predicted to be higher, these patients have not been studied separately so we cannot

comment specifically. However, patients with advanced stage disease, cachexia and significant comorbidity are less likely to undergo resectional surgery for cancer, and so would not have met the inclusion criteria for the individual studies. Additionally, it would have been ethically difficult to randomize participants with cachexia, as they often require preoperative artificial nutrition, and in such cases clinical equipoise would not have been reached. If cachectic or severely malnourished patients cannot be recruited into trials in which they could be randomized to a placebo or no supplements at all, then the only mechanism of establishing benefit is to study patients with varying degrees of malnutrition or no malnutrition at all. And, if as was found in this case, benefit is identified, it is possible that the benefit may be extrapolated to cachectic patients. Knight and colleagues[1] themselves suggest that the impact of IMN on infectious complications is likely to be underestimated in our meta-analysis due to inclusion of well-nourished patients. However, we would argue that this makes it more generalizable, because if IMN has a positive impact in well-nourished participants, then it would be expected to be even more beneficial in malnourished ones.

There are two suggestions that we hope are explored in the near future. First, a three arm trial comparing IMN with an isocaloric, isonitrogenous supplement and with a placebo in the same setting, with stricter definitions of infectious complications and surgical site infections in the current era of enhanced recovery protocols, should be undertaken to define the impact of IMN over and above a non-immune supplemented diet in patients having surgery for gastrointestinal cancer. Secondly, given the paucity of data from LMIC, where, as suggested, patients are more likely to be malnourished, it would be interesting to explore the effects of IMN in this setting.

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