404 words

Authors' response to Letters from Gunst et al (20-3415) and Lew et al (20-3583), CHEST

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SUMMARY CONFLICT OF INTEREST STATEMENTS:

DEB has received speaker fees, conference attendance support or advisory board fees from Nutricia, Baxter, BBraun, Nestle Nutrition, Fresenius Kabi, Abbott Nutrition, Cardinal Health and Avanos. ZP has received honoraria for consultancy from GlaxoSmithKline, Lyric Pharmaceuticals, Faraday Pharmaceuticals and Fresenius-Kabi and speaker fees from Orion and Nestle. HM holds patents relating to intravenous hydration and to regulation of metabolic efficiency using renin-angiotensin system antagonists and consults for Google Health. MW has accepted accommodation and attendance at educational meeting organised by Orion. Other authors have no conflicts of interest to declare.

Dear Editor,

We thank the authors of the above letters for their interest in and thoughtful comments regarding our trial of intermittent versus continuous feeding in the critically ill.

Muscle ultrasound does indeed underestimate muscle loss when compared to protein:DNA ratio[1]. Whilst local tissue oedema might contribute to such discrepancy, fluid status per se does not appear to be a confounder[2,3].

The respondents suggest that increased protein delivery in the intermittent feeding group may have worsened muscle loss, but the papers to which they refer relate to continuous feeding. Indeed, these observations (confirmed in our original paper) were what prompted us to test whether intermittent feeding may offer benefit over continuous amino acid provision. We agree that intermittent feeding may still be beneficial, but as stated, this is likely to be in the context of a multimodal intervention.

Both primary outcomes and adjusted analyses are appropriately powered, and details are provided in the manuscript and online supplement. No differences were seen between groups in withdrawal rates, and the risk of selection bias is low, given that our sensitivity analyses included use of imputation.

Daily median glucose and episodes of hyperglycaemia in the Per Protocol cohort are shown in Table 1. No differences were seen in baseline demographics between groups in this cohort (Table 2).

Both baseline and acute illness factors are likely to affect the nutrition/starvation response to autophagic flux[4,5]. We agree that the intervention may have been too short, in common with other critical care nutrition trials[6,7]. Future studies might extend beyond the ICU itself. As stated in the manuscript, we calculated feed delivery based on feeding days, which is appropriate for examination of the process of feed delivery[8].

Lew et al offer insightful comments on the leucine peak data. A direct comparison of plasma leucine concentrations (or percentage change) is not possible, given the different physiological and metabolic states between groups[9]. We currently do not know the bounds of leucinaemia in young or old critically ill patients. The higher doses of protein needed to sustain muscle protein synthesis in the study quoted only appear to occur when exercise is overlaid[10].

The fact that the two letters express diametrically opposed views on the role of nutritional protein in preserving muscle mass or provoking muscle wasting, demonstrates the equipoise on the role of current methods of nutritional support for the critically ill patient, and the need for trials such as the one we performed.

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Day	Intermittent arm	Hyperglycaemic episodes/day	Continuous arm	Hyperglycaemic episodes/day
0	8.5 (5.6-56.5)	0 (0-5)	8.4 (4.8-28)	0 (0-4)
1	9.5 (7.0-24.7)	2 (0-6)	8.4(4.8-25.4)	0 (0-6)
2	8.7(6.5-18.0)	1 (0-6)	8.6 (5.5-9.2)	0 (0-6)
3	9.1 (5.5-18.3)	1 (0-6)	8.3 (5.4-11.3)	0 (0-4)
4	8.8 (4.4-16.3)	1 (0-6)	8.7 (5.6-13.5)	0 (0-6)
5	9.1 (4.6-13.7)	1 (0-6)	8.5 (6.5-14.3)	0 (0-6)
6	9.2 (5.9-12.2)	2 (0-5)	8.7 (6.1-14.4)	0 (0-6)
7	8.4 (6.8-14.5)	1 (0-4)	8.1 (5.4-13.1)	0 (0-5)
8	9.5 (5.5-16.2)	2 (0-6)	8.4 (4.4-11.9)	0 (0-4)
9	8.6 (5.4-14.7)	1 (0-5)	7.9 5.2-13.9)	0 (0-5)
10	8.7 (4.9-12.8)	0 (0-4)	7.4 (6.0-14.6)	0 (0-5)

Table 1: Median (95%CI) glucose concentrations per day and median (range) hyperglycemic episodes per day during the 10-day trial period in per protocol cohort (n=63)

	Intermittent feeding (n=31)	**Continuous feeding (n=32)**	**p**
Age, y	55.1 (49.5-60.7)	61.3(55.6-66.9)	0.122
Male, No. (%) ¥	19 (61.3)	23 (71.8)	0.373
APACHE II score	23.2 (18.3-28.1)	19.2(16.3-22.2)	0.153
ICU LOS, d*	18 (9-84)	17.5 (6-52)	0.694
Hospital LOS, d*	32 (11-103)	34 (13-102)	0.416
SOFA score on admission	10.2 (9.1-11.3)	10.8 (9.7-11.9)	0.458
Comorbidities, No. (%)			
Hypertension	10 (32.3)	12 (37.5)	
Chronic Respiratory Diseases	11 (35.5)	8 (25.0)	
Diabetes Mellitus	10 (32.3)	7 (21.9)	
Ischemic heart disease	3 (9.7)	3 (9.4)	
Psychiatric diseases	9 (29.0)	3 (9.4)	

Renal impairment	2 (6.5)	3 (9.4)
Obesity	2 (6.5)	1 (3.1)
Liver cirrhosis	3 (9.7)	2 (6.3)
Haem-oncological disease	0 (0.0)	3 (9.4)
Thyroid disease	1 (3.2)	1 (3.1)
Crohns disease	0 (0.0)	1 (3.1)
Previous CVA	0 (0.0)	1 (3.1)

Table 2: Patient characteristics and demographics in per protocol cohort (n=63). ICU=Intensive Care Unit, APACHE II=Acute Physiology and Chronic Health Evaluation score, CVA=Cerebrovascular Accident, SOFA=Sequential Organ Failure Assessment, LOS=Length of Stay. Data are mean (95% confidence intervals) except for * (median and range), Student's T-test was used except for ¥ (Chi-squared) and * (Mann-Whitney U).