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Ensuring Optimal Survival and Post-ICU Quality of Life in High Risk ICU Patients: Permissive Underfeeding Is Not Safe!

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Keywords

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Great controversy has arisen recently between two differing opinions regarding optimal feeding in the ICU. Traditionally, it has been advocated that patients receive 80% of full calorie and protein (1.2-2.0 g/kg/d) feeds in the first week of ICU to optimize outcomes(1). However, a number of recent trials have advocated for “trophic feeding” or intentional underfeeding in the first ICU week being equally efficacious and perhaps beneficial (2-4). However, it is intuitive to most ICU practitioners that “all ICU patients are not created equal” and undoubtedly “one size does not fit all”. This concept is well described, in the article by Wei et al in this issue of Critical Care Medicine(5). The authors of this manuscript demonstrate that in high-risk ICU patients (mechanically ventilated > 8 days) receiving low nutritional adequacy in the first week of ICU stay (< 50 % of predicted caloric need) led to increased mortality (adjusted HR = 1.7, 95% CI: 1.1-2.6) versus patients receiving high nutritional adequacy (> 80% of calorie needs) after adjusting for key covariates.

The relationship of increased calorie delivery reducing mortality described in this data is in contrast to a number of recent studies of prescribed underfeeding or trophic feeding in the ICU. However, as “all patients are not created equal” there were significant differences between the patients studied in these trials of permissive underfeeding and trials like the Wei et al study showing clinical outcome benefits from adequate nutrition intake. As shown in table 1, patients in trials (2-4, 6)showing no benefit of reaching calorie goals in the first week of ICU stay (i.e. permissive underfeeding) were on average younger (55 y versus 63.25 y) and spent markedly less time on mechanical ventilation (6.125 days versus 9.8 days) versus patients in trials supporting clinical benefit of goal (> 80% of goal) calorie delivery(5, 7-9). Thus, it is likely that short staying ICU patients with lower acuity of organ dysfunction will not have as significant caloric needs as longer staying, more acutely ill ICU patients. This is supported by objective ICU nutrition risk scores showing ICU patients at high nutrition risk benefit more significantly from nutrition therapy then patients at lower

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risk(10). These scores demand further validation and implementation in ICUs worldwide. However, the challenge is that often even with an objective nutrition risk score it is difficult to predict which patients will remain on the ventilator for a prolonged period of time and become “long-stayers”. Thus, findings showing improved survival and quality of life from improved nutrition delivery (by avoiding purposeful underfeeding) such as those shown in this paper will need to be implemented in all patients with the possible realization that only the “long stayer” will benefit. This is vital in all patients as we know on average we only deliver 50% of the required caloric intake for our ICU patients for the first 12 days of ICU stay when practice is surveyed in ICUs worldwide(11). Finally, this adequate nutrition delivery can be achieved much more safely in the many patients who are failing to meet EN-goals early, as Total Parenteral Nutrition (TPN) has now been shown to *not be associated with an increased risk of infection* in any ICU patient studied in 3 recent large scale TPN trials using early full and supplemental TPN(7, 8, 12).

Although survival is still an important endpoint in ICU trials, recent thought leaders have indicated that future ICU trial endpoints should not focus on mortality as a primary endpoint, but on Post-ICU quality of life (QOL)(13). Recent data has shown that although we have reduced hospital mortality following sepsis by half, while sadly, we have tripled the number of patients going to rehabilitation following an ICU stay(13). Unquestionably, recent data shows interventions to improve ICU QOL are desperately needed(13, 14). Clearly, adequate nutrition delivery has been hypothesized to improve quality of life in ICU patients. Initial data from the EDEN trial in younger, short-staying, more obese ICU patients did not show an improvement in 12 month ICU QOL scores, although a trend towards improved 6-minute walk tests was observed(15). The data from Wei et al demonstrates that in older, long staying, higher risk ICU patients that for every 25% increase in calories delivered in the first week an improvement in Post-ICU QOL scores (as measured by the SF-36) was observed. Trends to improved QOL were also observed at 6 months. In Medical ICU patients (with often greater pre-illness comorbidities) the effect of improved nutritional adequacy on QOL was much stronger with significant improvements in 3 and 6 month SF-36 scores. These improvement in outcomes were not only quite statistically significant, but were also greater then the minimum clinical important differences (CIDs) for pulmonary disease(16). Experts in the ICU QOL field have extrapolated these CIDs in pulmonary disease to post-ICU quality of life as no CIDs for critical illness have been established(17). These CIDs for pulmonary disease are a change of 10 on the SF-36 scale for physical functioning and a 12.5 point change for role-physical(16). The data presented by Wie et al demonstrate that for every 25% increase in caloric delivery over the first 8 days in the MICU setting there is a 10.9 point increase in physical functioning and a 13.1 point increase in role-physical measures. Thus, a 50% or 75% increase in caloric delivery over the first week in the MICU setting would lead to a 20-30 point change in physical functioning and 26-40 point change in role-physical. These changes would equate to *large* change in QOL for ICU patients post-discharge based on previously established normal(16). At 6 months a 50% change in caloric delivery in the first 8 days would still reach the CID for clinically important improvement in physical QOL. Another recent ongoing trial by the ANZIC's group has shown that a 7.8 point change in physical QOL domain scores as considered clinically relevant based on their pilot trial data in post-ICU patients. Thus, these data

indicate that clinically significant changes in post-ICU QOL can be achieved by even a 25% increase in caloric delivery in the first 8 days of ICU stay(18).

Aside from being limited by the observational nature of the trial, another major limitation of the trial is the lack of correlation of post-ICU QOL with protein delivery. The authors correctly point out in this largely EN fed population protein delivery typically is given in a fixed ratio and as calories increase, protein does as well. A major differentiating factor in randomized clinical trials showing benefit in reaching goal nutrition delivery in table 1 versus trials not showing a benefit of reaching goal nutrition is that all the trials showing benefit reached a protein delivery of > 1.0 g/kg/d in the higher nutrition delivery group versus none of the trials reaching this goal in the trials showing no benefit or potential risk of trophic or permissive underfeeding. As protein is a fundamental building block of lean body mass, it will be vital to include protein delivery as a measure in nutrition intervention studies evaluating quality of life.

In conclusion, the risk of trophic or permissive feeding in the first week of ICU stay cannot be considered safe or indicated in older, higher risk ICU patients as it appears to increase mortality and impair long term quality of life. The greater concern is that we are currently unable to accurately predict the patients who will require prolonged mechanical ventilation or be the “long stayers”. Thus, any wide recommendation for trophic or permissive underfeeding in the first week of ICU stay may lead to harm in the long-staying ICU patient who will only reveal themselves when it is too late to make-up the calorie and protein debt they have acquired in the first week. Further research and implementation of ICU nutrition risk scores (i.e. NUTRIC score)(10) and direct bedside lean body mass analysis (i.e. ultrasound) to predict risk are needed in future trials to target high nutrition risk patients and as others have stated, post-ICU QOL must become a focus of all future ICU trial work.

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Table 1

	Trials Not Supporting Goal (>80% kcal/d) Nutritional Delivery in ICU				Trials Supporting Goal (> 80% kcal/d) Nutritional Delivery in ICU			
	EPaNIC NEJM, 2011	EDEN Trial (Pilot) CCM, 2011	Eden Trial (Full RCT) JAMA, 2012	Arabi Trial AJCN, 2011	Early PN, JAMA, 2013	TICACOS ICM, 2011	SPN, Lancet, 2013	Wei et al CCM, 2015
Age (Mean)	64	53	52	51	69	61	61	62
ICU LOS	3.5			13.1	9	12	13	18
Hospital LOS	15				25	25	31.5	
Mech. Vent Days	2	5.6	5	11.9	6.9	10.75	6.64	15
Mortality								
ICU	6.20%			19.60%		25.40%	10%	26%
Hospital	10.65%	21%		36%	21%	38.30%	24%	32%
Post-Discharge	11.20%		22.70%	38.60%		47%	23%	
Primary Outcomes	Sig. reduced LOS in ICU for Late PN (median 3d) vs. Early PN (median 4d)	No outcome changes in trophic versus full feeding groups for ventilation days, mortality, or infection	No outcome changes in trophic versus full feeding groups for ventilation days, mortality, or infection	Non-sig. trend to lower 28-d mortality for trophic (18.3%) compared with Target Feeding (23.3%) ($p < 0.07$)	No sig. change in crude day-60 mortality (standard care (22.8%) vs early PN (21.5%))	Sig. lower hospital mortality for goal calorie group (28.5% vs. underfed cont. group (48.2)	Sig. reduced nosocomial infections for EN+SPN (27%) vs. EN (38%) after day 9.	Sig. improved survival and 3 m HRQoL with improved nutrition delivery.
Secondary Outcome	Sig. higher infectious complications, duration of MV, and Hosp LOS for Early PN	Full feeding group more likely to be discharged home then rehabilitation unit ($p < 0.04$)	No Change in HRQoL at 12 m	No difference in LOS or Duration of MV	-Sig. shorter duration of MV, -Improved HRQoL for Early PN grp - No change in infection in PN vs EN	Longer duration of MV and ICU LOS, and higher infection rate for goal calorie study group	No sig. difference in the ICU LOS, Hosp. LOS, or mortality	Sig. improvement in HRQol in MICU pts at 3 and 6 m with improved nutrition delivery
Limitations	- > 50% of pts with short stays (< 3 d)	-Primarily young, obese pts with	-Primarily young, obese	- Very small difference in	- Many GI surgical pts	-Did not account for	- No difference in infections in	- Observational trial

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	and with no indication for nutrition.	and with no indication for nutrition.	pts with short duration of stay	caloric intake between trophic and full feeding group (~10% difference: 1067 ± 306 vs 1252 ± 432 kcal/d)		non-nutrition energy delivery	over entire study period	
	-Potential for overfeeding with glucose infusions in early PN group -Low protein intake (0.8 g/kg/d in all pts)	-Low protein delivery (0.8 g/kg/d) in both groups (including full feed group)	-Low protein delivery (0.6-0.8 g/kg/d) in both groups (including full feed group)	-Low protein intake (0.6 g/kg/d in all pts)		-Metabolic cart energy goals (may not be widely applicable currently)	-Metabolic cart energy goals (may not be widely applicable currently)	- Protein intake not able to be quantified

Abbreviations Used in Table: Sig.- Significant, HRQoL- Health Related Quality of Life, LOS- length of stay, PN- Parenteral Nutrition

-All time for length of stays and time of mechanical ventilation listed in days

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