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Nutrition therapy in Australia and New Zealand Intensive Care Units:

An international comparison study

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The authors have no conflicts to declare.

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ER, SP, AD, ARD, MJC and KL are all investigators on the TARGET trial.

AD is an employee of Baxter Healthcare Corporation, Australia. EJR has received unrestricted research funding for an investigator initiated study from Baxter Healthcare Corporation. AD and MJC are on the management committee for this study.

ABSTRACT:

Background: The Augmented versus Routine approach to Giving Energy Trial (TARGET) is the largest blinded enteral nutrition (EN) intervention trial evaluating energy delivery to be conducted in the critically ill. To determine the external validity of TARGET results, nutrition practices in intensive care units (ICUs) in Australia and New Zealand (ANZ) are described and compared to international practices.

Methods: Retrospective analysis of prospectively collected data for the International Nutrition Surveys, 2007-2013. Data are presented as mean (SD).

Results: 17,154 patients (ANZ: n=2776 vs. international n=14 378) were included from 923 ICUs (146 and 777 respectively). EN was the most common route of feeding (ANZ: 85%, n=2365 patients vs international: 84%, n=12 034, p=0.258) and EN concentration was also similar (<1.25kcal/ml ANZ: 70%, n=12 396 vs international: 65%, n=56 891 administrations, p<0.001). Protein delivery was substantially below the estimated prescriptions but similar between the regions (0.6 (0.4) g/kg/day vs 0.6 (0.4) g/kg/day, p=0.849). Patients in ANZ received slightly more energy (1133 (572) vs 948 (536) kcal/day, p <0.001), possibly because more energy was prescribed (1947 (348) vs 1747 (376) kcal/day, p<0.001), nutrition protocols were more commonly used (98% vs 75%, p<0.001) and included recommendations for therapies such as prokinetic agents (87%, vs 51%, n=399, p<0.001), and small bowel feeding (62% vs 40% p<0.001) compared to international ICUs.

Conclusions:

Key elements of nutrition practice are similar in ANZ and international ICUs. These data can be used to determine the external validity and relevance of the TARGET results.

Clinical relevancy statement:

The Augmented versus Routine approach to Giving Energy Trial (TARGET) is the largest blinded enteral nutrition intervention trial to be conducted in the critically ill. 4000 critically ill patients in Australia and New Zealand (ANZ) have been randomized to energy dense (1.5kcal/ml) enteral nutrition or routine care to evaluate whether increasing energy delivery effects clinical outcomes. To determine the external validity of the TARGET results we have compared ANZ and international nutritional practices. These data are important for critical care clinicians throughout the world to interpret the upcoming TARGET results.

INTRODUCTION

The provision of nutrition therapy to critically ill patients is a widely accepted international standard of care ¹⁻⁵. Practice guidelines assist clinicians to implement evidence based nutrition therapy and generally recommend that nutrition, delivered via an enteric tube (termed enteral nutrition (EN)), be started within 24-48 hours of admission to the intensive care unit (ICU) in the hemodynamically stable patient ¹⁻⁵. Delivery of nutrition in this way has been associated with reduced infective complications, length of ventilation, time in the ICU and mortality ¹⁻⁴. Beyond these elements however, there exists several areas of uncertainty due to lack of definitive evidence, specifically, the effect of nutrition risk, use of indirect calorimetry vs predictive equations, optimal timing of nutrition, the amount of energy and protein to provide, and how best to optimise nutrition delivery. This uncertainty leaves leaving recommendations contained in best practice guidelines open to significant interpretation and confusion.

One of the largest areas of area of uncertainty is the amount of energy to provide to critically ill patients to elicit optimum clinical outcomes. The Augmented versus Routine approach to Giving Energy Trial (TARGET) is the largest blinded enteral nutrition intervention trial evaluating energy delivery to be conducted⁶. The primary aim of this trial TARGET is to determine if augmentation of energy delivery using energy dense EN (a 1.5 kcal/ml EN solution) improves 90-day survival when compared to routine care. Whilst this trial is only being conducted in Australia and New Zealand (ANZ), the pragmatic nature of the intervention provides the opportunity for these data to be generalizable to international nutrition practice. It is however plausible that the current lack of definitive evidence regarding the role of energy and other key elements of nutrition practice in critical illness has resulted in significant temporal and geographical heterogeneity in practice. Thus, prior to the publication of TARGET and to establish external validity of the results, it is important to describe nutrition practices in ANZ and compare this to practice in international ICUs, with a focus on choice of EN solution and energy delivery.

METHODOLOGY

This was a retrospective analysis of data collected prospectively as part of the International Nutrition Survey (INS), a quality improvement activity coordinated by The Clinical Research Evaluation Unit (CERU), Ontario, Canada. Data were obtained for the survey annually from years 2007 to 2013 inclusive (with the exception of 2010 and there was no survey in 2012). The methods of this survey have previously been described in detail⁷. In summary, participation in the survey was voluntary, provided ICUs had at least 8 beds and a person with knowledge and ability to collect data. Available survey data included demographics on the hospital, ICU and nutrition service, as well as individual patient nutrition therapy

information for a maximum of 12 days. Consecutive patients who had mechanical ventilation initiated in the first 48 hours of ICU stay and remained in ICU for more than 72 hours were eligible for inclusion in the survey. Management of the patient was according to the individual clinicians in the ICUs. Data obtained for this analysis were: (1) hospital and ICU organisation details; (2) detailed nutrition assessment information (which was only collected in survey years 2011 and 2013); (3) daily nutrition provision information; and (4) outcome information.

Mode of nutrition therapy delivered on a study day was defined when a patient received EN, parenteral nutrition (PN) or oral nutrition alone or in any combination and each patient could contribute a minimum of 0 days and a maximum of 12 days. For each patient, a maximum of 3 unique EN solutions (as defined in the INS methodology) were collected during an EN study day (which have been defined as 'EN administrations' for the purpose of this analysis). Caloric content of EN solutions was confirmed using product information. If information was unavailable, it was unclear how the solution was being delivered or it was specifically designed to be a 'supplemental' product, the solution was excluded. EN solutions were grouped according to calorie content for analysis (kcal/ml): <1.25 (defined as standard EN solution); 1.25 to 1.49; 1.5 to 1.99; ≥ 2 . To simplify the description, methods to determine weight for the purpose of energy and protein estimations, and the choice of predictive equations were described as the most popular choice if $\geq 80\%$ of the patients underwent the same method at the site level and otherwise were defined as 'mixed' if the site did not report the same method for $\geq 80\%$ of the patients included in the analysis. Days where transition to permanent oral nutrition was noted have been excluded, as has day of discharge/death.

ICUs in ANZ were defined as those self-identified as being located in ANZ and international sites were defined as all other sites that did not identify as an ICU in ANZ.

Ethics approval for the larger survey was obtained by the CERU at Queens University, Canada and if required, by individual sites for each participating year of the survey. Further approvals were not required for this secondary analysis of data.

Statistical analysis

Categorical data are reported as numbers and percentages (%). Continuous data are reported as mean (standard deviation (SD)) where normally distributed or as median and interquartile range [IQR] where not normally distributed. Site characteristics are compared between regions using chi-square tests for categorical variables and 2-sample t-tests or Mann-Whitney tests for continuous data. Patient characteristics are compared using generalized estimating equations (GEE). Logistic and ordinal regression were used for categorical data and linear regression for continuous data, accounting for the clustering of patients within sites. Duration of mechanical ventilation and length of stay were censored at 60 days and log transformed for analysis. Time to discharge alive was censored at 60 days and analyzed via a log-rank test with death treated as a competing event. Analysis of EN administrations was done via a GEE logistic regression with clustering of administrations within patients, and patients within sites. Analysis was performed using SPSS version 22 and a two-sided p-value of 0.05 was considered to be statistically significant. Because sites may have participated in the survey in multiple years, a sensitivity analysis was repeated for energy and protein delivery only including data from the most recent survey from each site. Sensitivity analyses were also conducted to assess potential differences over the five survey years in the use of methods for estimating energy requirements and in the caloric content of EN administrations by including year and year-by-region fixed effects in the analysis models.

RESULTS

Overall site and patient characteristics

Patient characteristics are shown in Table 1 and site characteristics in Table 2. There were 923 ICUs in the data set from all survey years (146 from ANZ and 777 international), from 592 unique sites (70 from ANZ and 177 international) contributing 17 154 patients (2776 from ANZ and 14 378 international). Of sites from ANZ, 48% had participated once in the survey and 52% had participated multiple times, and for international sites it was 67% and 33% respectively.

Nutrition assessment

Overall, the mean percentage of patients per site in the analysis who received a nutrition assessment was 88% (26%) (n=7228). The mean proportion of patients who had a nutrition assessment was less in ANZ sites compared to international ICUs (80% (28%), n=75 vs 88% (25%), n=340 sites, p=0.001) and sites in ANZ were less likely to primarily use actual weights in energy estimations compared to international ICUs (13%, n=18, vs 30%, n=230 sites, p<0.001). The preferred methods to estimate energy requirements differed between ANZ and international ICUs; in ANZ ICUs, the Schofield equation⁸ and 'mixed methods' were the most common choices (both 33%, n=47) whereas in international ICUs the weight based energy estimation⁹ was the most common primary method (47%, n=385). There were no significant differences in usage over the 5 survey timepoints, except for the weight based energy estimation (year-by-region, p=0.016). When the weight based method was compared across years within each region the statistical differences did not remain (ANZ 34% in 2007 to 47% in 2013; International 51% in 2007 to 47% in 2013, p>0.95 for both).

The mean calorie and protein prescription differed between ICUs (Energy: 1947 (348) calories in ANZ vs 1747 (376) calories internationally, $p < 0.001$ and protein; 1.12 (0.25) g/kg/day in ANZ vs 1.17 (0.31) g/kg/day internationally, $p < 0.001$). Table 1 and 2 report further nutrition assessment information.

Mode of nutrition and choice of EN solution

EN was the most common mode of nutrition delivery overall (84%, $n = 14\,399$ patients) and this was similar across regions (ANZ: 85%, $n = 2365$ patients and international: 84%, $n = 12\,034$, $p = 0.258$) however EN was commenced earlier in ANZ; 19.3 [8-38] hours after admission compared to 28 [14-54] hours in international ICUs, $p < 0.001$. The percentage of patients receiving PN was also similar (ANZ: 20%, $n = 544$ and international: 21%, $n = 3024$, $p = 0.331$) but oral nutrition was provided more commonly in ANZ (43%, $n = 1196$ vs 31%, $n = 4476$ patients, $p < 0.001$). Figure 1 demonstrates combinations of nutrition therapy provided during the study period.

Information on caloric content was available in 90% ($n = 105\,515$) of the 117 891 EN administrations. Overall, the most commonly used EN solution in both ANZ (70% of administrations, $n = 12\,396$) and international ICUs (65% of administrations, $n = 56\,891$, $p < 0.001$) was a standard solution (< 1.25 kcal/ml). Figure 2 provides further data on EN solution preference. There was no significant change over time in the use of any caloric density in the sensitivity analysis (year-by-region interaction and year $p > 0.05$), with administrations of standard solution (< 1.25 kcal/ml) ranging from 71% in 2007 to 67% in 2013 in ANZ, and 68% in 2007 to 63% in 2013 internationally.

Adequacy of nutrition delivery

In ANZ patients, total energy delivery (from EN, PN and propofol) was slightly more than internationally (1133 (572) calories or 15 (8) kcal/kg/day vs 948 (536) calories or 13 (8) kcal/kg/day, $p<0.001$). However, protein delivery was similar in the two populations (46 (26) g or 0.6 (0.4) g/kg/day vs 44 (28) g or 0.6 (0.4) g/kg/day, $p=0.85$). Figure 3 shows daily energy and protein over the 12 day study period.

When excluding surveys from repeat contributing sites for the sensitivity analysis, the small point estimate differences between ANZ and international community for both energy delivery and protein became less (total energy 1086 (583) kcal/day or 14.0 (7.8) kcal/kg/day vs. 949 (538) or 13.2 (7.9); $p=0.064$; and total protein 44 (26) g/day or 0.57 (0.35) g/kg/day vs 44 (28) or 0.60 (0.39) g/kg/day, $p=0.131$)

Nutrition service

Nutrition therapy protocols were reported in 79% ($n=717$) of ICUs in the analysis but were more common in ANZ ICUs (98%, $n=143$ vs 75%, $n=564$, $p<0.001$) than those located internationally and the contents recommendations for management of nutrition significantly differed. ANZ ICUs more commonly reported the inclusion of prokinetic agents (87%, $n=127$ vs 51%, $n=399$, $p<0.001$), small bowel feeding tubes (62%, $n=90$ vs 40%, $n=314$, $p<0.001$), withholding of EN for clinical procedures (52%, $n=76$ vs 35%, $n=272$, $p<0.001$).

It was more common to have a dietitian in an ANZ ICU compared to an international ICU (93% vs 81%, $p=0.001$), however, if a dietitian was present, the mean full time equivalent

(FTE) per 10 beds was lower in ANZ sites compared to international sites (0.32 (0.20) vs 0.46 (0.32) FTE), $p < 0.001$). Further nutrition service information can be viewed in Table 2.

Interruptions to EN delivery

EN was interrupted in more ANZ patients than internationally (72%, $n=1695$ vs 59%, $n=7103$, $p < 0.001$), with the most common reason being for a procedure (ANZ: 69%, $n=1173$ vs 61%, $n=4361$, $p < 0.001$) (Table 3).

Clinical outcomes

Clinical outcome data are shown in Table 4.

DISCUSSION

Summary of main findings

This is the first study to compare nutrition practice in ANZ to international practice. Overall, differences were observed in nutrition assessment techniques, nutrition service and delivery details, however many of these were modest. The route of delivery and the type of EN formula used were similar between regions. Energy delivery was slightly higher in ANZ ICUs, but significantly below predicted energy requirements in both regions. This may be because predicted energy requirements were higher and practice within ANZ more frequently utilised a protocol which included elements recommended in best practice guidelines to increase energy delivery, or, there may be population characteristics which are contributing. While differences were observed, they were modest, and such observations are important as

in general, they support the external validity of TARGET results and can be used in interpretation and application of the findings.

How does this fit with current literature?

Sites in ANZ prescribed and delivered higher amounts of energy compared to international sites; however, the overall provision of energy and protein in both regions remained substantially less than the estimated requirements. The delivery of less than recommended energy and protein during critical illness is a consistent observation regardless of region investigated and/or different survey data are used¹⁰⁻¹³. Importantly, this establishes that the group randomised to receive routine care in TARGET, as identified in the pilot trial, represents standard practice within ANZ and internationally¹⁴. Several practice issues have previously been described as contributing to nutrition inadequacy in critical illness and may be contributing in this analysis; interruptions to EN (which were frequently observed in this study and a feature of nutrition therapy guidelines in ANZ ICUs); delayed initiation of nutrition; and gastrointestinal intolerance^{15, 16}. An alternate explanation for the persistent nutrition inadequacy may be that clinicians have decided to stop advocating for meeting nutrition goals beyond that achieved in standard care until definitive evidence is available regarding the optimal energy and protein target in critical illness.

A standard concentration (<1.25kcal/ml) EN solution was the most commonly prescribed solution in both ANZ and international sites. The frequent use of a standard concentration EN solution has previously been documented in observational data from ANZ¹⁷. Although there was a slightly higher use of standard formulae in the ANZ group, which was statistically

significant due to the large numbers analysed, the difference was numerically inconsequential.

Implications for clinical practice and research

This study demonstrates that the use of a standard concentration EN solution (<1.25kcal/ml) is the most commonly used formula and that delivery of energy and protein is substantially below estimated requirements throughout the world. The exact amount of energy and protein to be delivered (and how this relates to an estimated or measured target) is one of the fundamental unanswered questions in critical care nutrition; TARGET will be the largest blinded enteral nutrition trial conducted in the critically ill and will thus provide important evidence as to the role of energy delivery during the acute phase of critical illness. If provision of energy close to recommended goal is beneficial in critical illness, the strategy applied in TARGET (which delivers a 1.5 kcal/ml EN solution at the same goal rate as a 1 kcal/ml solution) has the potential to be widely adopted without a major change in feeding principles¹⁴. Finally, this study has identified that in ANZ there is a considerable proportion of patients ingesting oral nutrition, with or without supplemental tube liquid enteral nutrient. This poses a new challenge for clinicians in both practice and research. Little is currently understood regarding the management and optimisation of oral intake during critical illness, with several small studies indicating significant difficulties for multifactorial reasons^{18, 19}. This remains to be investigated in future work.

There are several plausible explanations for the difference in energy delivery observed between the two regions, which should be considered when interpreting the results. The

increased energy delivery in ANZ patients may be due to differences in specific aspects of nutrition management and the patient population. Compared to international ICUs, sites in ANZ reported greater dietitian presence and more use of nutrition protocols. The protocols more commonly included elements associated with improved nutrition delivery as recommended by best practice feeding guidelines. The differences in protocol content may account for the shorter time to commencing EN and the increased prescribed and delivered energy in the ANZ cohort, however evidence for the role of nutrition protocols in both increasing energy delivery and in improving clinical outcomes is conflicting^{20,21}. This may thus explain the observation of varied existence and content of nutrition therapy protocols. Further, the lack of definite evidence in many areas of critical care nutrition practice makes definitive practice recommendations difficult and may also contribute to the differing contents reported in protocols. Alternatively, the higher proportion of overweight and obese patients in ANZ compared to international ICUs may also account for the higher energy delivery (due to the higher energy aim).

Strengths and limitations

This a large dataset that provide valuable information of international and ANZ specific nutrition delivery and informing the generalizability of future nutrition trials conducted in ANZ such as TARGET. There are however some potential limitations. This study was observational and uses data that were collected for quality improvement activities. As such, the data collection is unlikely to be as robust as that collected as part of a clinical trial and we were limited by the information available. Further, this was a retrospective analysis and is therefore subject to the limitations associated with an analysis of this type. Many ICUs participated over multiple years, and when adjusted for in a sensitivity analysis the moderate

difference between ANZ and international energy and protein delivery were even less. Accordingly, ANZ ICUs interested in nutrition may have been more likely to participate in the survey and therefore exacerbate any differences that exist. It must also be noted that in the analysis, all ICUs from regions outside of ANZ were grouped together to form the international cohort. Regions that are larger may therefore be influencing the results more than smaller regions, and there may also be differences in practice between smaller regions which were not described with this method. Nutrition risk in critically ill patients may influence the prescription and response to artificial nutrition therapy^{22, 23}. We were unable to assess any relationship between prescription practices and nutrition risk due to limited survey data on nutrition risk. And importantly, practice may have changed since the last and over the duration of the survey years, with the first survey being performed 10 years ago and the last, 5 years ago. Despite this possibility, the data from the INS is the largest and most comprehensive data available to inform on current nutrition therapy practice. Finally, it is also possible that different practices in medical management and service delivery which were not collected as part of the survey explain some of the differences between the two regions, such as greater energy delivery and proportion of patients receiving oral nutrition.

It must also be acknowledged that due to the size of the database, many variables were statistically significant in their comparisons but were not always clinically important. Specifically, the energy difference observed (187 kcal/day or 2 kcal/kg/day) was relatively minor and it seems intuitively unlikely that such a difference will result in meaningful improvements in patient centered outcomes. This must be considered in the interpretation of the results.

The data also suggest that the cohort in ANZ may be less unwell than the international cohort, supported by more favourable clinical outcomes in the ANZ population, although many of the differences were modest and probably statistically significant only due to the size of the sample. This may also partially explain better energy delivery in the ANZ cohort; clinicians may have prioritised nutrition delivery earlier and/or EN tolerance may have been greater in a less sick cohort. These slight differences in population should however be considered when applying the results of the TARGET trial to populations outside of ANZ.

CONCLUSION

Differences were observed in nutrition assessment, service and delivery between ANZ and international ICUs; however, such differences were modest and while statistically significant they may not be clinically meaningful. Overall, key elements of nutrition practice in ANZ that relate to design aspects of TARGET appear sufficiently similar to international practice to ensure external validity and relevance of the TARGET results to the international community.

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Figure 1: Mode of nutrition delivery during study period ANZ:

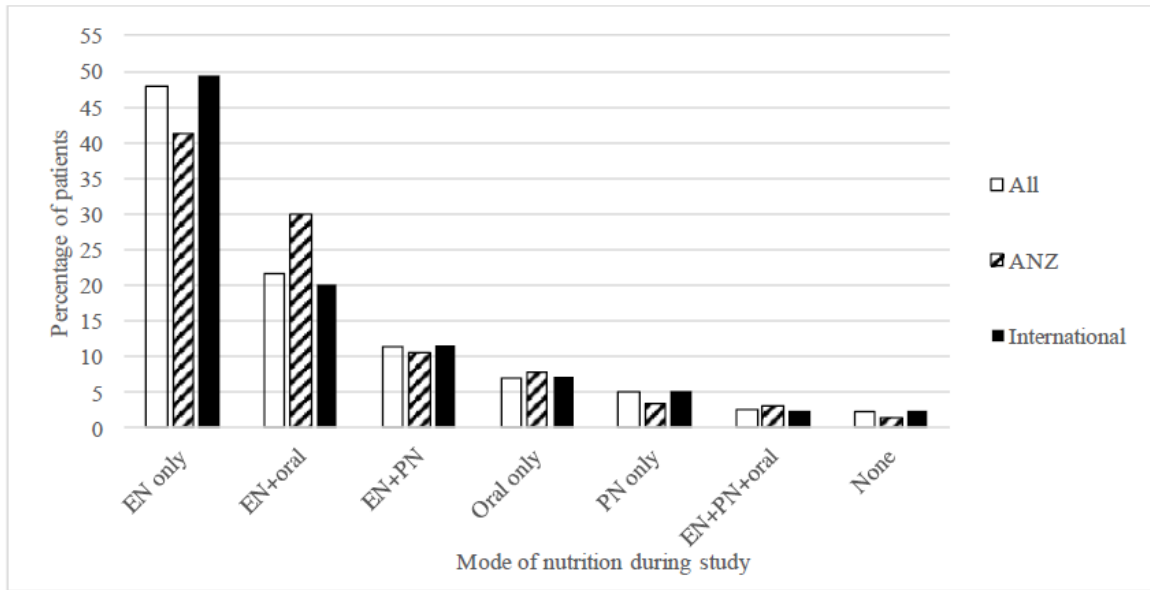
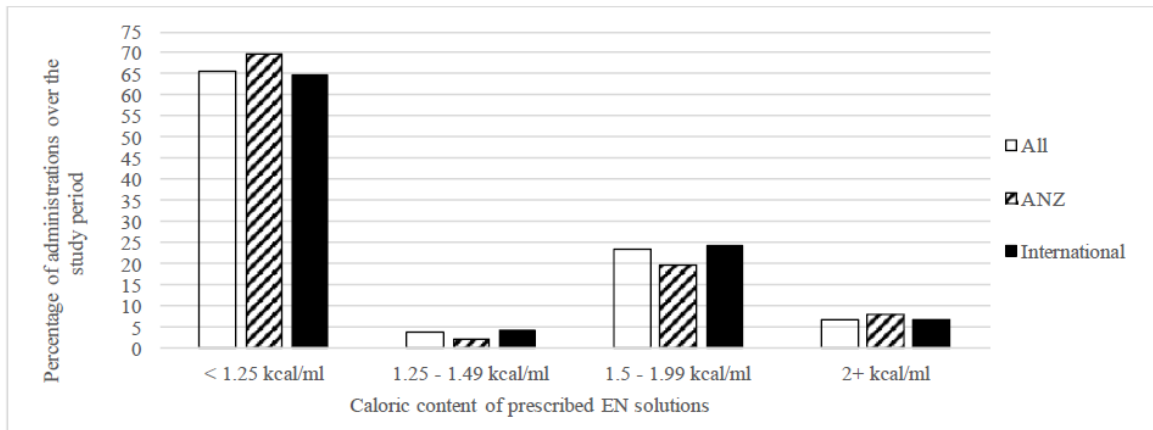


Figure 2: Caloric content of prescribed EN solutions during the study period



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Figure 3: Daily energy (Panel A) and protein delivery (Panel B) over the study period from all sources in the whole cohort, Australia and New Zealand and international Intensive Care Units. Data is presented as mean (SE).

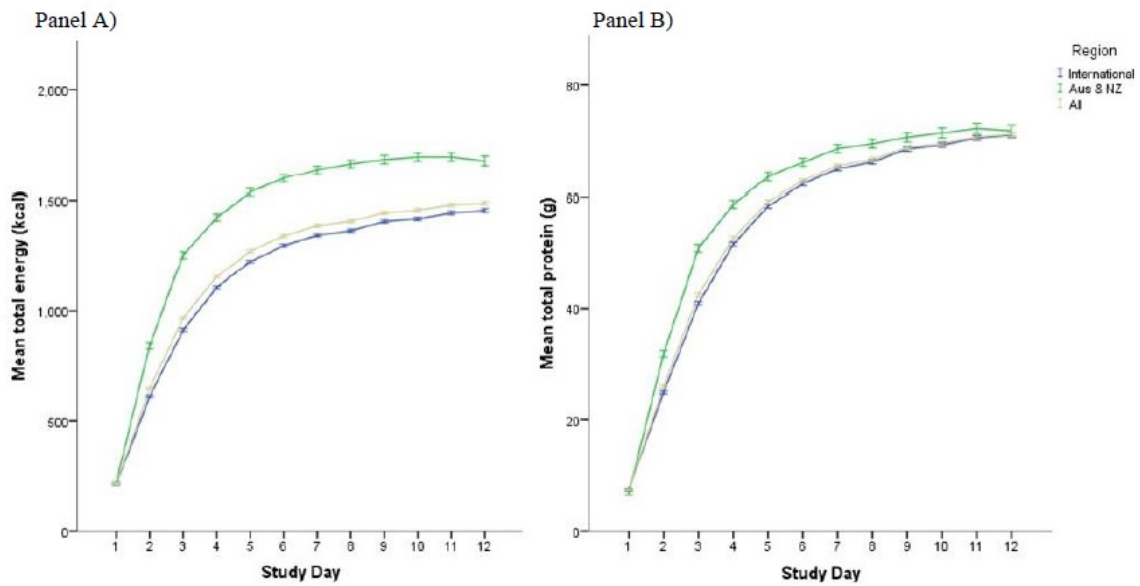


Table 1: Patient characteristics

Characteristic	Overall n=17 154	ANZ N=2776	International N=14 378	P-value
Proportion of patients by site location, n (%)				
ANZ	2776 (16)			
Canada	3231 (19)			
USA	4906 (29)	n/a	n/a	n/a
Europe & Sth Africa	2403 (14)			
Latin America	1270 (7)			
Asia	2568 (15)			
Age, years, mean (SD)	60 (18)	58 (18)	60 (18)	<0.001
Gender, male, n (%)	10 347 (60)	1737 (63)	8610 (60)	0.011
BMI, kg/m ² , mean (SD)	27 (8)	28 (7)	27 (8)	0.003
Underweight (<18.5 kg/m ²), n (%)	863 (5)	109 (4)	754 (5)	<0.001
Normal (18.5-24.9 kg/m ²), n (%)	6849 (40)	968 (35)	5881 (41)	
Overweight (25-29.9 kg/m ²), n (%)	4965 (29)	901 (33)	4064 (28)	
Obese (30+ kg/m ²), n (%)	4393 (26)	775 (28)	3618 (25)	
Admission type, n (%)				
Medical	10866 (63)	1612 (58)	9254 (64)	0.003

Surgical emergency	4140 (24)	720 (26)	3420 (24)	
Surgical elective	2147 (13)	444 (16)	1703 (12)	
Admission Diagnosis, n (%)				
Medical: Respiratory	4151 (24)	526 (19)	3625 (25)	<0.001
Surgical: Gastrointestinal	1896 (11)	364 (13)	1532 (11)	0.009
Medical: Sepsis	1643 (10)	209 (8)	1434 (10)	0.001
APACHE II Score, median (IQR)	22 (16-27)	21 (16-26)	22 (17-27)	0.021
Energy and protein requirements, mean (SD)				
Prescribed energy requirements (kcal/day)	1780 (379)	1947 (348)	1747 (376)	<0.001
Prescribed energy requirements (kcal/kg/day)	24 (6)	25 (5)	24 (6)	<0.001
Prescribed protein requirements (g/day)	88 (25)	87 (21)	88 (26)	0.851
Prescribed protein requirements (g/kg/day)	1.16 (0.30)	1.12 (0.25)	1.17 (0.31)	<0.001

APACHE: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index; IQR: Interquartile range; kcal: Kilocalorie; SD: Standard deviation

Table 2: Site and nutrition assessment characteristics (data is by site)

Characteristic	Overall n=923	ANZ N=146	International N=777	P-value
Location of international sites, n (%)				
Canada			171 (19)	
USA			270 (29)	
Europe & Sth Africa	n/a	n/a	129 (14)	n/a
Latin America			64 (7)	
Asia			143 (16)	
Hospital size, beds, mean (SD)	595 (407)	525 (225)	608 (432)	0.540
ICU size, beds, mean (SD)	18 (10)	16 (8)	18 (10)	0.390
Contents of feeding protocol, yes, n (%)				
Head of bed elevation	562 (61)	79 (54)	483 (62)	0.067
GRV, ml, mean (SD)	246 (90)	242 (79)	247 (92)	0.364
BGL and insulin protocol, yes, n (%)	795 (86)	113 (77)	682 (88)	<0.001

BGL targets in protocols, mmol/L, mean (SD)				
Upper	8.5 (1.6)	8.9 (1.4)	8.4 (1.7)	0.004
Lower	4.9 (1.2)	5.0 (1.3)	4.9 (1.2)	0.562
Weight used in energy estimation, n (%)				
Actual	248 (27)	18 (13)	230 (30)	<0.001
Estimated	40 (4)	8 (6)	32 (4)	0.472
Ideal based on BMI 20-25kg/m ²	46 (5)	9 (6)	37 (5)	0.489
Mixed-use	511 (57)	97 (67)	414 (54)	0.004
Method to estimate energy requirements, n (%)				
Schofield Equation ⁷ with adjustment for stress and/or activity	66 (7)	47 (33)	28 (3)	<0.001
Weight based ⁸	426 (44)	41 (29)	385 (47)	<0.001
Mixed-use	268 (28)	47 (33)	221 (27)	0.360

EN: Enteral nutrition; ICU: Intensive care unit; kcal: Kilocalorie; SD: Standard deviation

Table 3: Nutrition delivery information (data is by patient)

Characteristics	Overall n=17 154	ANZ N=2776	International N=14 378	P-value
Energy and protein delivery from EN during study period, mean (SD)				
Energy from EN (kcal/day)	745 (553)	855 (596)	724 (542)	<0.001
Protein from EN (g/day)	36 (28)	38 (27)	36 (28)	0.075
Percentage of energy and protein requirements provided during the study period, mean (SD)				
Energy requirements met by EN	42 (31)	44 (30)	42 (31)	0.095
Protein requirements met by EN	42 (31)	44 (30)	42 (31)	0.111
Energy requirements met by EN+PN+propofol	56 (30)	59 (28)	55 (30)	0.006
Protein requirements met by EN+PN	52 (30)	53 (28)	52 (31)	0.205
EN interrupted during study, yes, n (%)	8796 (61)	1695 (72)	7103 (59)	<0.001
Reasons for interruptions, n (%)				
Fasting for procedure	5534 (63)	1173 (69)	4361 (61)	<0.001
Intolerance to EN	2291 (26)	418 (25)	1873 (26)	0.129
Other	2328 (26)	405 (24)	1923 (27)	0.387

Duration of interruptions to EN, hours, mean (SD)				
Total duration of EN interruptions	22 (18)	23 (19)	21 (18)	0.224
Duration of EN interruptions per 24	2.4 (1.9)	2.6 (2.0)	2.4 (1.9)	0.045

EN: Enteral nutrition; ICU: Intensive care unit; PN: Parenteral nutrition; kcal: Kilocalorie; SD: Standard deviation

Table 4: Outcomes

Characteristics	Overall	ANZ	International	P-value
Mortality to 60 days, died, n (%)				
ICU	3299 (19)	383 (14)	2916 (20)	<0.001
Hospital	4360 (25)	557 (20)	3803 (26)	<0.001
Duration of mechanical ventilation, days, median [IQR]	7[3-15]	6 [3-12]	7 [3-16]	<0.001
Length of stay, days				
ICU	10 [6 -19]	9 [5-17]	11 [6-20]	0.001
Hospital	24 [13-52]	26 [14- 49]	24 [13-53]	0.212
Time to discharge alive				
ICU	16 [7 – undefined]	11 [6- 28]	14 [7 – undefined]	<0.001
Hospital	38 [16-undefined]	34 [16- undefined]	40 [16 – undefined]	<0.001

ICU: Intensive care unit; IQR: Interquartile range;