The effect of intermittent or continuous feeding and amino acid concentration on urea-to-creatinine ratio in critical illness

Luke Flower MBChB[1,2*], Ryan W. Haines MBBS[2,3*], Angela McNelly PhD[3,4,5], Danielle E. Bear PhD [6,7,8] Kiran Koelfat MD[9], Steven Olde Damink PhD[9,10], Nicholas Hart PhD [8,11], Hugh Montgomery MD[4,5], John R. Prowle PhD[3,12,13], Zudin Puthucheary PhD[3,13]

These authors contributed equally to this work.

[1]Honorary Fellow, William Harvey Research Institute, Queen Mary University of London, London, UK [2]Department of Anaesthesia, University College Hospital, 235 Euston Road, London, UK [3]William Harvey Research Institute, Queen Mary University of London, London, UK [4]University College London (UCL), [5]UCL Hospitals NHS Foundation Trust (UCLH), National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), London, [6]Department of Nutrition and Dietetics St Thomas' NHS Foundation Trust , [7]Department of Critical Care, Guy's and St. Thomas' NHS Foundation & King's College London (KCL) NIHR BRC, London, [8] Centre for Human and Applied Physiological Sciences, Kings College London, [9]Department of Surgery and School of Nutrition and Translational Research in Metabolism (NUTRIM), University of Maastricht, Maastricht, The Netherlands, [10]Department of General, Visceral and Transplantation Surgery, RWTH University Hospital Aachen, Germany, [11]Lane Fox Clinical Respiratory Physiology Research Centre Guy's and St. Thomas' NHS Foundation & King's College London (KCL) NIHR BRC, London, [12]Department of Renal Medicine and Transplantation, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, E1 1BB, UK, [13]Adult Critical Care Unit, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, UK.

Correspondence and requests for re-prints to:

Dr Zudin Puthucheary

Adult Critical Care Unit

The Royal London Hospital

Barts Health NHS Trust

Whitechapel Road

London

United Kingdom e-mail: z.puthucheary@gmul.ac.uk

Tel: +44 7767357983

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ABSTRACT

Background

We sought to determine whether peaks in essential amino acid concentration associated with intermittent feeding may provide anabolic advantages when compared to continuous feeding regimens in critical care.

Materials and Methods

We performed a secondary analysis of data from a multicentre trial of UK intensive care patients randomised to intermittent or continuous feeding. A linear-mixed-effects model was developed to assess differences in urea-creatinine-ratio (raised values of which can be a marker of muscle wasting) between arms. To investigate metabolic phenotypes, we performed k-means urea-to-creatinine ratio trajectory-clustering. Amino acid concentrations were also modelled against urea-to-creatinine ratio from day 0 to day 10. The main outcome measure was serum urea-to-creatinine ratio from day 0 to the end of the 10-day study period.

Results

Urea-to-creatinine ratio trajectory differed between feeding regimens (coefficient -0.245, p = 0.002). Patients receiving intermittent feeding demonstrated a flatter urea-to-creatinine ratio trajectory. With K-means analysis, the cluster with the largest proportion of continuously fed patients demonstrated the steepest rise in urea-to-creatinine ratio. Neither protein intake per se nor serum concentrations of essential amino acid concentrations were correlated with urea-to-creatinine ratio (coefficient = 0.088, p = 0.506; and coefficient <0.001, p = 0.122, respectively).

Conclusion

Intermittent feeding can mitigate the rise in urea-to-creatinine ratio otherwise seen in those continuously fed, suggesting that catabolism may have been to some degree prevented.

Clinical Trial Registry: www.ClinicalTrials.gov: NCT02358512

Clinical Relevance Statement

Muscle wasting affects more than 50% of critically ill patients. To date no treatment strategies have been effective in attenuating this impact. Intermittent (rather than continuous feeding, as is routinely practiced) causes cyclical peaks in serum essential amino acid concentration, which may promote muscle protein synthesis. Using urea-to-creatinine ratio as a biomarker of critical illness catabolism, we show that intermittent feeding may indeed help limit catabolism. Further work is required to explore the functional impacts of such an intervention, especially if combined with other anabolic approaches, and the patient groups who might benefit most.

Introduction

Acute muscle wasting affects more than 50% of patients and is associated with an increase in mortality and morbidity. [1,2–4] Muscle loss occurs rapidly (2-3% a day) and is the result of an imbalance in muscle protein synthesis (MPS) and muscle protein breakdown (MPB).[2,4,5] To date, no single intervention has been found effective in reducing this process in critical illness.[6–10]

The anabolic effect of essential amino acid (EAA) delivery, and specifically that of leucine, has been proposed as a mechanism through which muscle wasting may be reduced, with increased MPS observed following their ingestion in a healthy population.[11] However, this response is quickly saturated due to the 'muscle full effect', with further EAA no longer increasing MPS.[12] This may contribute to the ineffectiveness of current *continuous* delivery of enteral tube feed in preventing muscle wasting.[11,13] As an alternative, *intermittent* feeding might more closely replicate the cyclical concentrations seen in normal dietary patterns.[14] The resultant EAA concentration peaks promote an anabolic state and increased MPS in healthy subjects.[14] Intermittent feeding also results in altered ghrelin, insulin and YY peptide concentrations, potentially increasing amino acid availability and promoting MPS.[14–16]

In a randomised trial of intermittent vs. continuous feeding, intermittent feeding did not mitigate ultrasound-assessed loss of rectus femoris muscle cross-sectional area in critical illness, although nutritional targets were better met.[14] However, this technique may have been less sensitive to impacts on muscle mass, whilst intermittent feeding may advantageously affect protein metabolism in ways not detectable at the whole muscle level.[2,14]

The rise in amino acid release associated with muscle catabolism leads to a decrease in serum creatinine concentration, secondary to loss of muscle mass. It also releases amino acids which drive increased urea cycle activity and thus ammonia production.[17,18] The ratio of concentration of serum urea to that of creatinine (UCR) is thus a long-established marker of muscle wasting, of specific value in the critically ill.[17–21]

We thus undertook a secondary analysis of the intermittent vs. continuous (IVC) trial data to compare the effects of intermittent or continuous enteral feeding on the serum concentrations of urea and creatinine, and on UCR. In addition, we assessed the relationship between leucine and the non-essential amino acids that feed into the urea cycle (figure 1), and UCR.

Methods

Study design and participants

The IVC study (NT02358512) was a multicentre single-blinded randomised controlled trial.[14] Participants from 8 UK intensive care units (ICU) were randomised (1:1 ratio, concealed allocation, figure S1) to receive continuous or intermittent enteral feed. The characteristics and demographics of patients randomised to each limb were well balanced.[22] The original study received ethics committee approval (National Research Ethics Service Committee London-Queens Square; REC reference 14/LO/1792; IRAS project ID 160281) and was registered on clinicaltrials.gov before randomisation was commenced.[14] Patients were required to have been admitted to the ICU for $\leq$ 24 hours prior to enrolment. Included were patients ≥18 years of age who were anticipated to

be mechanically ventilated for >48 hours, required enteral feeding via a nasogastric tube, had multi-organ failure (Sequential Organ Failure Assessment (SOFA) score >2 in ≥2 domains at admission), had a likely ICU stay of >7 days, and who were considered likely to survive >10 days.

Study procedures

On recruitment, patient age, weight, medical history and APACHE II score on admission to ICU, were recorded. Daily nutritional and biochemical data for the 10 day intervention (including volume of enteral feed received, energy and protein targets, urea and creatinine levels), and requirement for renal replacement therapy) were documented. The intermittent feeding regimen (the intervention) consisted of six feeds per 24 hours; each administered over three to five minutes via nasogastric tube. The continuous (standard) feeding regimen delivered nasoenteral feed continuously over 24 hours, as per local guidelines. More details on the feeding regimens can be found in the supplement and the original publication.[17] UCR was calculated as serum urea concentration (mmol/litre) divided by serum creatinine (mmol/litre), in mmol/mmol. Plasma concentrations of EAA and non-essential amino acid (NEAA) were included from measurements on day 1 and 7. Concentrations of plasma free amino acids were determined by reversed phase high-performance liquid chromatography. Samples were deproteinized with 5-suflosalicylic acid, frozen immediately and stored at -80◦C. Samples were thawed at 4◦C and centrifuged at 50,000 x g prior to analysis.

Outcomes

The primary outcome was UCR trajectory from randomisation (day 0) through to day 10. As a sensitivity analysis, we assessed patient characteristics based on UCR trajectory-clusters. As a secondary analysis, we correlated total serum amino acid (AA), EAA and individual serum AA concentrations with serum UCR concentrations.

Data analysis

Statistical analysis was performed with R version 4.0.0. Continuous data are represented using median and interquartile range and are compared using Wilcoxon signed rank test. As this is an exploratory re-analysis of a previous trial, no formal sample size calculation was performed.

Assessment of difference in UCR trajectories between feeding regimens was performed using a linear mixed effect model following logarithmic transformation.[14,23] Linear mixed effects models are able to analyse repeated measures data, allowing for both random and fixed effects, and are robust at handling missing data via the use of maximum likelihood estimation. Within our model, differences in patients' baseline UCR and UCR trajectories throughout the trial were incorporated as random effects. Fixed effects included enteral feeding regimen received, the use of renal replacement therapy, patient age, protein/kg of bodyweight, c-reactive protein (CRP) and SOFA score on admission. We used restricted cubic spline to allow for non-linearity of change in UCR over time.

Amino acid analysis was performed using a second mixed effects model. Total amino acid, total essential amino acid, glutamine, asparagine, citrulline, arginine, and leucine concentrations were all individually modelled against the corresponding day 1 and day 7

logUCR (as these were the days amino acid concentrations were recorded), with random baseline UCR incorporated as random effects.

K-mean trajectory clustering was performed using an unsupervised machine learning technique, based on logUCR values.[14] Patients were assigned to a cluster dependent on their trajectory and the clinical characteristics between clusters were then compared.

Results

Patient demographics

Of the 121 patients included, 62 were in the intervention (IF) group, and 59 in the control (continuous feeding) group. In total 63 patients completed the full 10-day trial period (table 1).[14] The UCR was analysed in 113 patients who had data recorded, and the amino acid analysis on the 84 patients with AA data available. Patients in the intermittent feeding group received a higher percentage of their protein targets than those in the continuous feeding group (80.3% vs. 69.9%, p = <0.001).[17,18]

Raw urea-to-creatinine ratio unadjusted for clinical variables

A difference in UCR trajectory was demonstrated between the two feed groups (p = 0.016) (Figure 2). Day 0 urea was not significantly different between the continuous and intermittent feeding groups (7.9 [IQR 4.2 – 10.9] vs. 9.1 [IQR 5.7 – 15.25] respectively, p 0.776) and neither was creatinine (88.5 [69.75 – 175.50] vs. 108 [70.0 – 188.0] respectively, p 0.410). Day 0 UCR was also not significantly different between the continuous and

intermittent group (67.0 [IQR 50.0 – 95.6 vs. 81.0 [IQR 58.3 – 106]] respectively, p 0.111). UCR in the continuous feeding group reached a higher peak than that in the intermittent feeding group (Figure 2, figure S2 & S3). The median increase in UCR between the continuous and intermittent groups at day 10 failed to reach statistical significance (63.91 [IQR 24.28 – 112.24) compared to 31.30 [IQR 12.98 – 59.58]), p = 0.066). At day 10, median [IQR] UCR values for the continuous group were similar to that in the intermittent group (130.5 [IQR 95.9 – 181.2] vs. 135.0 [IQR 78.18 – 179.3] respectively, p 0.915).

Urea-to-creatinine ratio adjusted for clinical variables using linear mixed effects modelling

The model demonstrated different UCR trajectories between feeding groups, with the continuous feeding group demonstrating a steeper positive gradient than the intermittent feeding group, with a cross-over point between days 5 and 6 given the higher initial UCR (Figure 2).

For continuous vs. intermittent feeding groups, the model predicted a median [95% confidence interval] day 5 UCR of 105.636 [93.691 – 119.104] vs. 108.853 [96.544 – 122.732], and a day 10 UCR of 135.639 [112.168 – 164.022] vs. 127.741 [106.698-152.933] respectively. A higher amount of protein received per kg of actual body weight was not associated with an increased UCR across the whole 10-day period (coefficient = 0.088, 95% CI -0.170 – 0.345, p = 0.506) or specifically after day 5 following the crossover of UCR trajectories (coefficient = 0.195, 95% CI -0.150 – 0.540, p = 0.271). Neither was this true of SOFA score on admission (coefficient = -0.009, 95% CI: -0.031 – 0.013, p = 0.426).

Increasing patient age was associated with a small increase in UCR (coefficient = 0.052, 95%

CI: 0.001 – 0.009, p = 0.017), as was a lower CRP (coefficient = -0.0002, 95% CI: -0.004 – 0.000), p = <0.001) (table 2). The use of RRT was associated with a significant reduction in UCR for both groups (coefficient -0.325, 95% CI -0.463 – -0.188, p < 0.001) (Figure 3).

Clustering analysis

In the unsupervised machine learning k-means analysis, patients were split into three separate clusters (A, B, and C), with varying baseline UCR and trajectories (Figure 4). Cluster A followed a gradually increasing UCR trajectory, with 27 (60%) allocated to the intermittent feeding arm. Cluster C followed a more rapidly increasing UCR trajectory, with 5 (30%) allocated to the intermittent feeding arm. Cluster B demonstrated a consistently low UCR trajectory, with patients predominantly allocated to the intermittent feeding arm (63%) and the majority of patients in this cluster (72%) received RRT, table S1.

Amino acid analysis

The amino acid model analysis demonstrated no association between day 1 or day 7 serum UCR and total essential and non-essential amino acid concentration or with specific amino acids proximal to the urea cycle (glutamine, citrulline, arginine) or leucine concentration. Asparagine concentrations did appear to correlate with a lower logUCR (coefficient = -0.004, 95% CI -0.008 – 0.000, p = 0.039) on day 1 but not on day 7 (Supplementary table 2).

Discussion

Summary of findings

In this study we found that intermittent enteral nutrition potentially attenuates the rise in UCR Seen in the critically ill, when compared to standard (continuous) feeding. This finding

was supported by unsupervised machine learning k-means analysis, in which the cluster with the highest proportion of patients receiving continuous feeding demonstrated the steepest increase in UCR throughout the 10 days, with intermittent feeding being associated with a flatter trajectory. Finally, in our amino acid analysis no clear correlation was found between day 7 UCR and total or individual AA or EAA concentration. Asparagine showed a correlation with day 1 UCR which could be a chance finding, in view of the absence of correction for multiple comparisons. As expected, RRT significantly reduced UCR trajectory over the time course of critical care admission, with k-means analysis suggesting that the use of RRT was associated with a consistently low UCR.

Interpretation of findings

Rising UCR is increasingly recognised as a catabolic signature in critical illness,[17] being associated with muscle wasting in this group.[14] This study showed different magnitudes of increasing UCR across patients, consistent with previous reports of rising UCR in patients admitted to ICU. UCR rose more slowly in the intermittent feeding group throughout the 10-day period despite greater protein delivery. Recent work by McNelly et al. looked specifically into the effects of continuous feeding and intermittent feeding on critical illness associated muscle wasting and nutritional delivery.[14] Intermittent feeding did not prevent muscle wasting, though the intermittent feeding group were more likely to attain nutritional targets.[4]

This study suggests intermittent feeding and continuous feeding affect UCR trajectory differently, with a steeper rise in UCR seen with continuous feeding. The differential longitudinal trajectory of a catabolic signature could reflect differences in protein metabolism between groups (in terms of tissue uptake versus ureagenesis). Importantly,

these data suggest intermittent feeding may be useful as one of several interventions to prospectively test as a strategy to address acute muscle wasting.

Despite potentially greater catabolism at baseline, the relatively flat UCR trajectory seen in the intermittent feeding group after randomisation may reflect diminished muscle catabolism thereafter, with less amino acid breakdown resulting in a lower rise in urea over time and accompanied by a smaller fall in creatinine generation. This flat trajectory implies that the protein delivered was not diverted to ureagenesis, and therefore potentially taken up by tissues. This is insufficient to generate new muscle mass, likely due to intramuscular hypoxia and inflammation.[24] This may, hypothetically be advantageous as these amino acids would then be available for recovery, in conjunction with the anabolic scaffolding that has been demonstrated to develop in preparation for recovery.[24]

Intermittent feeding may impact UCR by several mechanisms. The potential peaks in EAA concentration, increase in splenic blood flow and alteration in ghrelin, insulin and YY peptide seen may all increase amino acid availability and MPS. This may result in reduced amino acid catabolism, decreased urea cycle activity and thus a lower UCR or smaller rise overtime.

Potential confounders of UCR were addressed during the analysis. The presence of heart failure, dehydration, upper gastrointestinal bleeding (UGIB), and acute kidney injury (AKI) all impact UCR. Randomisation meant that on admission there was no significant difference in the prevalence of AKI or cardiac failure between the two groups, and no upper gastrointestinal bleeds were recorded in either of the groups. There is also no reason why either continuous or intermittent feeding would preferentially cause cardiac failure, dehydration or an UGIB during the study period.

Whilst changes in urea and creatinine are affected by kidney function, their ratio is less affected as reductions in their excretion will be similarly decreased. Tubular injury in AKI may

dampen the change in UCR due to altered concentrating capacity, but this would attenuate rather than accentuate any changes seen in our study.[17] RRT will lessen any changes in UCR due to its equimolar removal of urea and creatinine in the extracorporeal circuit.[17] As a consequence, the use of RRT was accounted for in modelling.

We were unable to demonstrate a direct relationship between plasma concentrations of amino acids proximal to the urea cycle and UCR, nor with Leucine. This may be the result of the small numbers of data points, though these data represent one of the larger data sets of combined longitudinal AA concentrations with detailed clinical data in critically ill patients.

Study implications

This study demonstrates a significant difference in UCR between intermittent feeding and continuous feeding regimens, with the use of continuous feeding associated with reduced protein delivery and a greater increase in serum UCR over time. UCR has been recognised as a marker of catabolism for some time, with recent work specifically highlighting its role as a catabolic signature in critical illness. UCR may therefore which may help stratify patients most at risk from critical illness associated muscle wasting, and intermittent feeding can ameliorate the rise in UCR in patients with multi-organ failure. Importantly, these data suggest IF, in addition to enhancing delivery of feed, results in an increase in amino acid uptake adding to the body of evidence that intermittent feeding may be considered as part of a bundle of interventions for the prevention of muscle wasting. Further research is needed to demonstrate this, and that reducing the UCR results in improvement of patient centred outcomes.

Strengths and weaknesses

Our study has several limitations. First, this was not a prespecified secondary analysis and the original trial was not originally designed with UCR as an outcome measure increasing the risk of bias in these observational findings. Nevertheless, we used robust methods to maximise information from repeated measures data and a secondary unsupervised machine learning approach supported our findings. Second, baseline UCR was higher in the intermittent feeding group and since this occurred before randomisation it cannot be a treatment effect, but a baseline imbalance due to the chance because of the relatively small sample size. However, we were able to model the effect of different baselines and still demonstrated difference in trajectories over the time course of study. Importantly, we did not constrain these relationships to a linear change but instead used restricted cubic splines to enhance modelling of change in UCR over time.

Conclusions

An intermittent enteral feeding regimen can potentially alter the trajectory of the Urea-to-Creatinine ratio, a catabolic signature, when compared to continuous enteral feeding. This is despite achieving greater protein delivery, suggesting a possible higher uptake of amino acids into tissue as opposed to diversion to ureagenesis. Further research is required to confirm these findings and investigate if this results in improvements in patient relevant outcome measures.

Tables and figures

Table 1 –Patient characteristics and demographics

Characteristic	All	Intermittent Feeding	Continuous Feeding	*P* Value
	(N = 121)	(n = 62)	(n = 59)	
Age, y	57.7 (54.7-60.6)	55.2 (51.0-59.3)	60.3 (56.0-64.1)	0.086
Male, No. (%) [a]	81 (66.9)	41 (66.1)	40 (67.8)	0.997
Urea (95% CI)	10.63 (-2.835 - 24.095)	11.21(-3.627 - 26.047)	9.89 (5.80)	0.004
Creatinine (95% CI)	121.84 (95.34)	125.7 (96.37)	116.98 (93.92)	0.168
UCR	103.13 (5.62 - 200.64)	105.38 (4.832 - 203.678)	100.32 (47.66)	0.174
Protein - gkg (95% CI)	0.77 (0.241 - 1.299)	0.79 (0.320-1.260)	0.75 (0.30)	0.011
LOS before ICU admission, d [b]	0.0 (0-15)	0.0 (0-15)	0.0 (0-15)	0.259
Period ventilated, d [b]	7.3 (0.5-48)	9.5 (0.5-48)	6.0 (0.63-43)	0.249
ICU LOS, d [b]	13.0 (0.7-93)	13.0 (0.7-93)	12.0 (1.5-52)	0.626
Hospital LOS, d [b]	22.8 (1.5-183)	22.0 (1.7-183)	26.0 (1.5-102)	0.907
APACHE II score	21.8 (19.9-23.6)	23.1 (19.9-26.2)	20.2 (18.2-22.3)	0.134
SOFA score on admission	10.4 (9.7-11.0)	10.3 (9.4-11.2)	10.6 (9.6-11.5)	0.709
ICU survival, No. (%) [a]	87.0 (71.9)	44.0 (71.0)	43.0 (72.9)	0.173
Hospital survival, No. (%) [a]	79.0 (66.4)	39.0 (63.9)	40.0 (69.0)	0.571
RRT, No. (%)	43.0 (36.8)	25.0 (41.7)	18.0 (31.6)	0.338
NMBA use, d [b]	0.0 (0-9)	1.0 (0-9)	0.0 (0-7)	0.109
Admission diagnosis, No. (%)				
Sepsis	47 (38.8)	21 (33.9)	26 (44.1)	
Cardiogenic shock	27 (22.3)	16 (25.8)	11 (18.6)	
Trauma	14 (11.6)	6 (9.7)	8 (13.6)	
Respiratory failure	9 (7.4)	6 (9.7)	3 (5.1)	
Intracranial hemorrhage	6 (5.0)	3 (4.8)	3 (5.1)	
Acute liver failure	5 (4.1)	2 (3.2)	3 (5.1)	
Acute kidney Injury	4 (3.3)	3 (4.8)	1 (1.7)	
Drug overdose	4 (3.3)	3 (4.8)	1 (1.7)	

Emergency surgery	3 (2.5)	1 (1.6)	2 (3.4)	
Cerebrovascular accident	2 (1.7)	1 (1.6)	1 (1.7)	
Comorbidities, No. (%)				
Hypertension	44 (36.4)	24 (38.7)	20 (33.9)	
Chronic respiratory diseases	39 (32.2)	23 (37.1)	16 (27.1)	
Diabetes mellitus	32 (26.4)	20 (32.2)	12 (20.3)	
Ischemic heart disease	18 (14.9)	11 (17.7)	7 (11.9)	
Psychiatric diseases	23 (19.0)	12 (19.4)	11 (18.6)	
Renal impairment	8 (6.6)	2 (3.2)	6 (10.2)	
Obesity	10 (8.3)	6 (9.7)	4 (6.8)	
Liver cirrhosis	9 (7.4)	3 (4.8)	6 (10.2)	
Haem-oncologic disease	9 (7.4)	6 (9.7)	3 (5.1)	
Thyroid disease	5 (4.1)	3 (4.8)	2 (3.4)	
Crohn's disease	3 (2.5)	2 (3.2)	1 (1.7)	
Previous CVA	2 (1.7)	1 (1.6)	1 (1.7)	
Chronic pancreatitis	1 (0.8)	1 (1.6)	0 (0.0)	

Data represent mean (95% CI), unless indicated otherwise. The Student t test was used unless indicated otherwise. APACHE II = Acute Physiology and Chronic Health Evaluation; CVA = cerebrovascular accident; LOS = length of stay; NMBA = neuromuscular blockade agent; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.

Table 2 – Primary analysis results: linear mixed effects model (n = 121).

Day:feed – restricted cubic spline of feed over time. Other variables incorporated as fixed effects within the model.

CRP – c-reactive protein; RRT – Renal replacement therapy, SOFA – sequential organ failure assessment score.

Variable	**Coefficient**	**Standard error**	**t-value**	**p-value**	**95% CI**	
Day:Feed (knot 1)	0.303	0.103	2.949	0.003	0.101	0.505
Day:Feed (knot 2)	0.369	0.201	1.836	0.070	-0.025	0.763
Day:Feed (knot 3)	0.263	0.140	1.873	0.060	-0.012	0.537
Feed	-0.245	0.100	-2.451	0.016	-0.441	-0.049
RRT	-0.254	0.081	-3.148	0.002	-0.411	-0.096
CRP	-0.0002	0.000	-2.128	0.034	0.000	0.000
SOFA	-0.009	0.012	-0.800	0.426	-0.032	0.013
Protein intake (g/kg)	0.088	0.131	0.668	0.506	-0.170	0.345
Age	0.005	0.002	2.296	0.024	0.001	0.009

Figure legends:

Figure 1: The urea cycle

ASL – argininosuccinate lysas; ASS1 – arginosuccinate synthase; ARG1 – arginase; CPS1 – carbamoyl phosphate synthetase; OTC – ornithine crabamoyltransferase

Figure 2: Predicted values of logUCR split by feed from the linear mixed effects model.

Feed 0 – intermittent feeding regimen; feed 1 – continuous feeding regimen

Figure 3: Predicted values of logUCR split by use of renal replacement therapy.

rrt 0 – no renal replacement therapy; rrt 1 – received renal replacement therapy.

Figure 4: Unsupervised k-means clusters of longitudinal urea-to-creatinine trajectories. Number of patients allocated to the intermittent feeding regime for each cluster were as follows; cluster A = 27 (60%), cluster B = 25 (64%), and cluster C = 5 (30%).

Supplementary tables

Table S1 – KML cluster breakdown

Table S2 – Amino acid coefficients table

Supplementary figures

Figure S1 – Patient flow chart

Figure S2 – Raw UCR vs day box plot

Figure S3 – Histogram of urea and creatinine measurements for each regimen

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