Online-Only Supplement:

Intravenous amino acid therapy for kidney function in critically ill patients: A randomized controlled trial

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for the Nephro-Protective Trial Investigators Group.

The Nephro-Protective Trial

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Contents

Note: *Additional information can be found at the study web site: www.EvidenceBased.net/NephroProtect*

THE NEPHRO-PROTECTIVE TRIAL INVESTIGATORS

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Complete eligibility criteria:

To be applied within the first two days of study ICU admission.

Inclusion Criteria

Patients will be considered ***eligible*** for the trial if ***all*** of the following *inclusion criteria* are met at the time of screening:

1) Is the patient currently on their First or Second calendar day of admission to the study ICU?

2) Is the patient expected to remain in the study ICU today and tomorrow?

3) Does the patient have a working central venous access line through which the study intervention could be delivered?

4) Is the patient able to tolerate at least 1L of fluid volume per day?

[The study intervention may involve the delivery of up to one litre of amino acids per day. This volume of amino acids can replace equivalent volumes from other fluids being received.]

5) Is the patient 18 years of age or older?

See next page for Exclusion Criteria.

Exclusion Criteria

Patients will be considered ***ineligible*** for the trial if ***any*** of the following *exclusion criteria* are met at the time of screening: (Answer **NO** to all questions)

Note: The Exclusion criteria are continued over two pages:

1) Is the patient currently receiving an NSAID with specific emphasis on COX-2 inhibitors?

['*Currently receiving*' means the patient will continue to receive the NSAID or COX-2 inhibitor during their ICU stay. If the patient does NOT plan to continue receiving one of these drugs daily, they may be enrolled: the COX-2 inhibitors Celecoxib, Paracoxib, Etoricoxib or > 160mg Aspirin or any dose of Ibuprofen, Naproxen, Piroxicam, Indomethacin, Meloxicam, Mefenamic Acid, Diclofenac, Prioxicam, Ketoprofen, Tiaprofenic Acid, Ketorolac.]

2) Is the patient currently enrolled into a clinical trial evaluating a nitric oxide (NO) inhibitor?

3) Is the patient currently receiving Acetazolamide, which is a diuretic that works on the proximal tubule?

4) Is the patient's current serum creatinine greater than the allowable age and gender adjusted maximum reported in the Maximum Creatinine Table? (see page 19)

5) Does the patient have severe Acute Kidney Injury, defined as:

Current serum creatinine (SCr) increased 3 times pre-acute illness value OR

SCr >350 μmol/L with recent increase greater than 44 μmol/L?

[**Note**: If pre-acute illness creatinine values are unknown, assume upper limit of normal: 90 μmol/L for females and 110 μmol/L for males.]

6) Is the patient currently receiving or scheduled for dialysis / renal replacement therapy?

7) Has the patient ever had a kidney transplant?

8) Is the patient expected to receive palliative care only and is not expected to survive ICU or hospital discharge?

9) Is the patient moribund and not expected to survive 24 hours?

10) Is the patient brain dead or suspected to be brain dead?

Continued on next page.....

Exclusion Criteria *continued*

Patients will be considered ***ineligible*** for the trial if ***any*** of the following *exclusion criteria* are met at the time of screening: (Answer **NO** to all questions)

11) If the patient has been admitted to the study ICU directly from another ICU, is the total number of calendar days from other ICU admission until today greater than two calendar days?

12) Does the patient require treatment of a burn injury to greater than 20% of total body surface area?

13) Has the patient been taking Nardil (phenelzine) within the last 6 weeks?

[Nardil (phenelzine) is an uncommonly used anti-depressant. It may be used in people who are resistant to other treatment for major depression or anxiety disorders. Because of its unique side-effect profile, and explicit drug interactions (meperidine, epinephrine, norepinephrine), a history of Nardil (phenelzine) use is usually found clearly documented in the patient's charts.]

14) Has the patient previously been enrolled and randomised into this study?

15) Does the patient have a documented contraindication to the study intervention (IV amino acids), as listed on the TGA product licensing document?

Australian Therapeutic Goods Association Product Licensing Contraindications, Synthamin 17 EF:

(Answer **NO** to all questions)

15A. Is the patient known to be pregnant or currently breastfeeding?

15B. Does the patient have severe liver disease (Biopsy proven cirrhosis, or documented portal hypertension with a known past history of either upper GI bleeding attributed to portal hypertension or of hepatic failure leading to encephalopathy / coma)?

15C. Does the patient have a documented hypersensitivity (known allergy) to one or more of the included amino acids?

[Known allergies will be clearly documented in the Patient's Charts. See Product Details for complete list of Ingredients.]

15D. Does the patient have a documented inborn error of amino acid metabolism?

[Ex. Phenylketonuria (PKU), Maple Syrup Urine Disease. These disorders are actively screened for during childhood. If present, they will be clearly documented in the patient's charts and will likely be accompanied by strict directions to consult a Dietitian prior to providing nutritional support. Other less common inborn errors include: atypical phenylketonuria, hereditary tyrosinaemia, biotinidase deficiency, methylmalonic aciduria, glutaric acidemia, methylglutaconic acidemia.]

<end exclusion criteria>

Maximum Creatinine Table

Age and Gender adjusted maximum allowable creatinine for enrolment.

See Exclusion Criteria 4.

Females										
Age (years)	*18*	*19*								
serum Creatinine (μmol/L)*	284	282								
Age (years)	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*
serum Creatinine (μmol/L)	279	277	274	272	270	268	266	265	263	261
Age (years)	*30*	*31*	*32*	*33*	*34*	*35*	*36*	*37*	*38*	*39*
serum Creatinine (μmol/L)	260	258	257	255	254	253	252	250	249	248
Age (years)	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*	*49*
serum Creatinine (μmol/L)	247	246	245	244	243	242	241	240	239	238
Age (years)	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*
serum Creatinine (μmol/L)	237	237	236	235	234	234	233	232	231	231
Age (years)	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*
serum Creatinine (μmol/L)	230	229	229	228	227	227	226	226	225	224
Age (years)	*70*	*71*	*72*	*73*	*74*	*75*	*76*	*77*	*78*	*79*
serum Creatinine (μmol/L)	224	223	223	222	222	221	221	220	220	219
Age (years)	*80*	*81*	*82*	*83*	*84*	*85*	*86*	*87*	*88*	*89*
serum Creatinine (μmol/L)	219	218	218	217	217	216	216	215	215	215
Age (years)	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*98*	*99*
serum Creatinine (μmol/L)	214	214	213	213	213	212	212	211	211	211
Age (years)	*100*	*101*	*102*	*103*	*104*	*105*	*106*	*107*	*108*	*>109*
serum Creatinine (μmol/L)	210	210	209	209	209	208	208	208	207	203

Males										
Age (years)	*18*	*19*								
serum Creatinine (μmol/L)	368	365								
Age (years)	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*
serum Creatinine (μmol/L)	361	358	355	353	350	347	345	343	341	338
Age (years)	*30*	*31*	*32*	*33*	*34*	*35*	*36*	*37*	*38*	*39*
serum Creatinine (μmol/L)	336	335	333	331	329	327	326	324	323	321
Age (years)	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*	*49*
serum Creatinine (μmol/L)	320	318	317	316	315	313	312	311	310	309
Age (years)	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*
serum Creatinine (μmol/L)	308	306	305	304	303	302	301	301	300	299
Age (years)	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*
serum Creatinine (μmol/L)	298	297	296	295	294	294	293	292	291	291
Age (years)	*70*	*71*	*72*	*73*	*74*	*75*	*76*	*77*	*78*	*79*
serum Creatinine (μmol/L)	290	289	288	288	287	286	286	285	284	284
Age (years)	*80*	*81*	*82*	*83*	*84*	*85*	*86*	*87*	*88*	*89*
serum Creatinine (μmol/L)	283	283	282	281	281	280	280	279	278	278
Age (years)	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*98*	*99*
serum Creatinine (μmol/L)	277	277	276	276	275	275	274	274	273	273
Age (years)	*100*	*101*	*102*	*103*	*104*	*105*	*106*	*107*	*108*	*>109*
serum Creatinine (μmol/L)	272	272	271	271	270	270	269	269	269	264

Study intervention: Dosing algorithm for supplementary amino acids

If randomised to the intervention arm, the patient received a continuous infusion of a standard mixture of L-amino acids (Synthamin 17 Electrolyte Free, Baxter Healthcare, Australia) delivered at a rate to achieve a total daily protein intake of approximately 2.0 g/kg/day.

The initial infusion was begun at approximately 100 g/day. If the patient was receiving any form of enteral or parenteral nutritional support, the infusion rate of the study L-amino acid intervention (study Synthamin 17 EF) was reduced such that the total protein intake from all sources (nutrition and study intervention) was approximately 2.0g/kg/day.

The study intervention was discontinued at discharge from the study ICU, or death, or when the patient's central venous catheter was removed.

Study nephroCALC web tool and Synthamin 17 EF infusion protocol

(https://Research.EvidenceBased.net/nephroCALC, see eAppendix 1 for screen capture)

The nephroCALC study web tool calculated study Synthamin 17 EF infusion rates based on a patient's current protein intake from Enteral and Parenteral nutrition and the patient's weight. Protein intake calculations for overweight (BMI > 25 kg/m^2) patients were based on their ideal body weight (ideal BMI set at 23 kg/m^2).

The majority of patients commenced study Synthamin 17 EF at an infusion rate of 42 ml/h, which provided 100g amino acids per day.

The protocol reduced the Synthamin 17 EF infusion to a lower rate **only** if total protein from EN, PN and study Synthamin 17 EF reached 2.5g/kg.

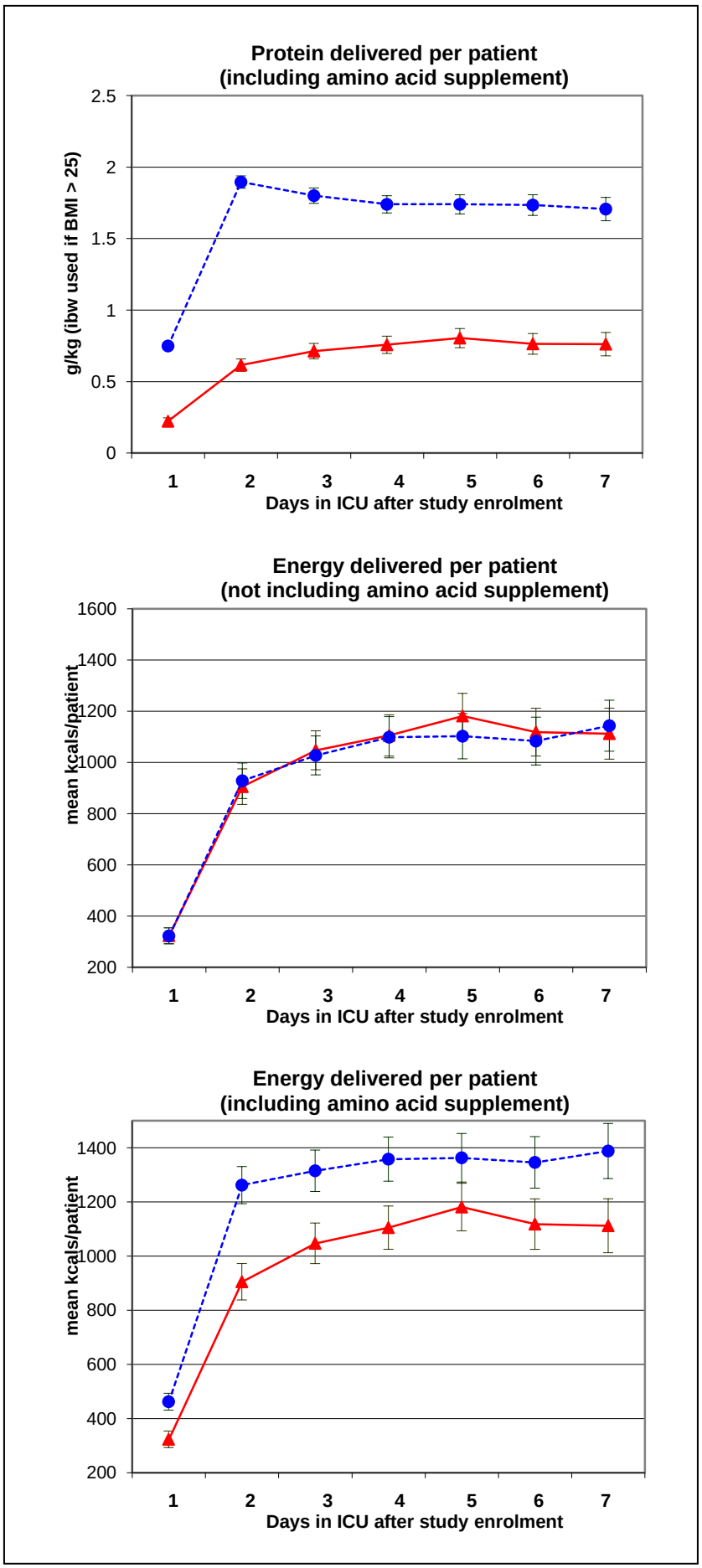
If total protein from EN, PN and study Synthamin 17 EF reached 2.5g/kg, the Protocol reduced the patient's study Synthamin 17 EF infusion rate such that a total protein intake of 2.0g/kg from EN, PN and study Synthamin 17 EF was achieved.

The nephroCALC study web tool was used to conduct all calculations. Results were printed or written on to a blank form to create a permanent record of calculations. It was the site investigator's responsibility to ensure that the appropriate study Synthamin 17 EF infusion rates, as calculated by the nephroCALC web tool, were effectively communicated to, and achieved by, the bedside health care team.

If a patient switched to a different brand of EN or a different type of PN, or if EN or PN was started or discontinued, the nephroCALC study web tool was used to calculate a *new* study Synthamin 17 EF infusion rate.

The nephroCALC study web tool was not password protected. It could be accessed by the bedside nurse on the weekend / at night if required.

eFigure 1. Study process measures: Nutrition support



Amino acid supplement (n=239)

Standard Care (n=235)

Error bars indicate 95% confidence intervals around differences between groups.

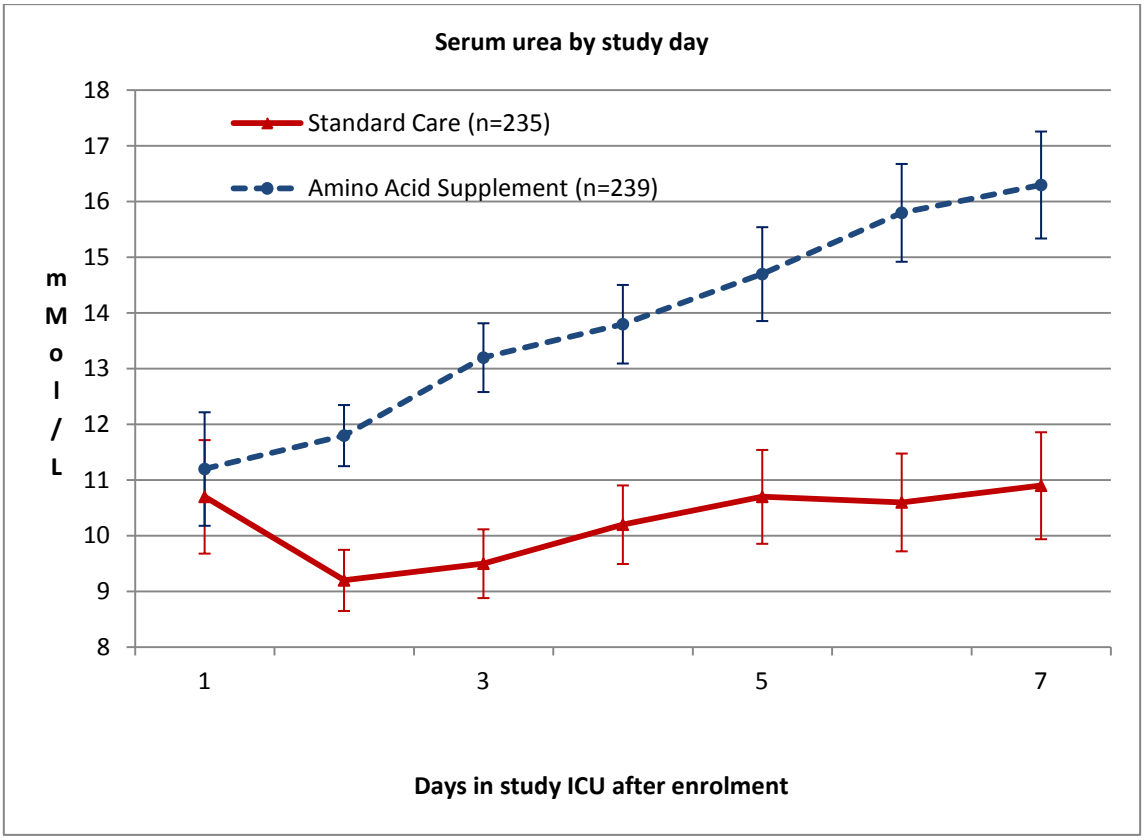
ibw: ideal body weight; **BMI:** Body Mass Index

eTable 1: Patient characteristics on day of initiating RRT

	Standard Care 13 patients	**Amino Acid Supplement** 25 patients	***p-value***
Time from study enrolment to RRT, days, mean (SD)	5.5 (7.4)	4.5 (3.8)	*0.65*
Creatinine, mean (SD) μMol/L	359 (169)	278 (123)	*0.11*
Fluids administered, mean (SD), All fluids, mL/24 h	2942 (2238)	3667 (2955)	*0.18*
Total urine output, mean (SD) mLs/24 h,	285 (107)	1291 (830)	*0.0002*
Oliguria, n (%) < 100mLs over 6 consecutive hours.	12 (92.3%)	15 (60.0%)	*0.06**
Potassium, mean (SD) mMol/L	5.3 (1.1)	4.7 (0.6)	*0.08*
Urea, mean (SD) mMol/L	21.4 (7.0)	29.9 (13.5)	*0.02*
Urea > 30 mMol/L, n (%)	1 (7.7%)	10 (40%)	*0.06**
Arterial pH, mean (SD)	7.36 (0.13)	7.26 (0.08)	*0.15*

***** Exact p-value; **RRT:** renal replacement therapy; SD: standard deviation

eFigure 2: Serum urea by study day

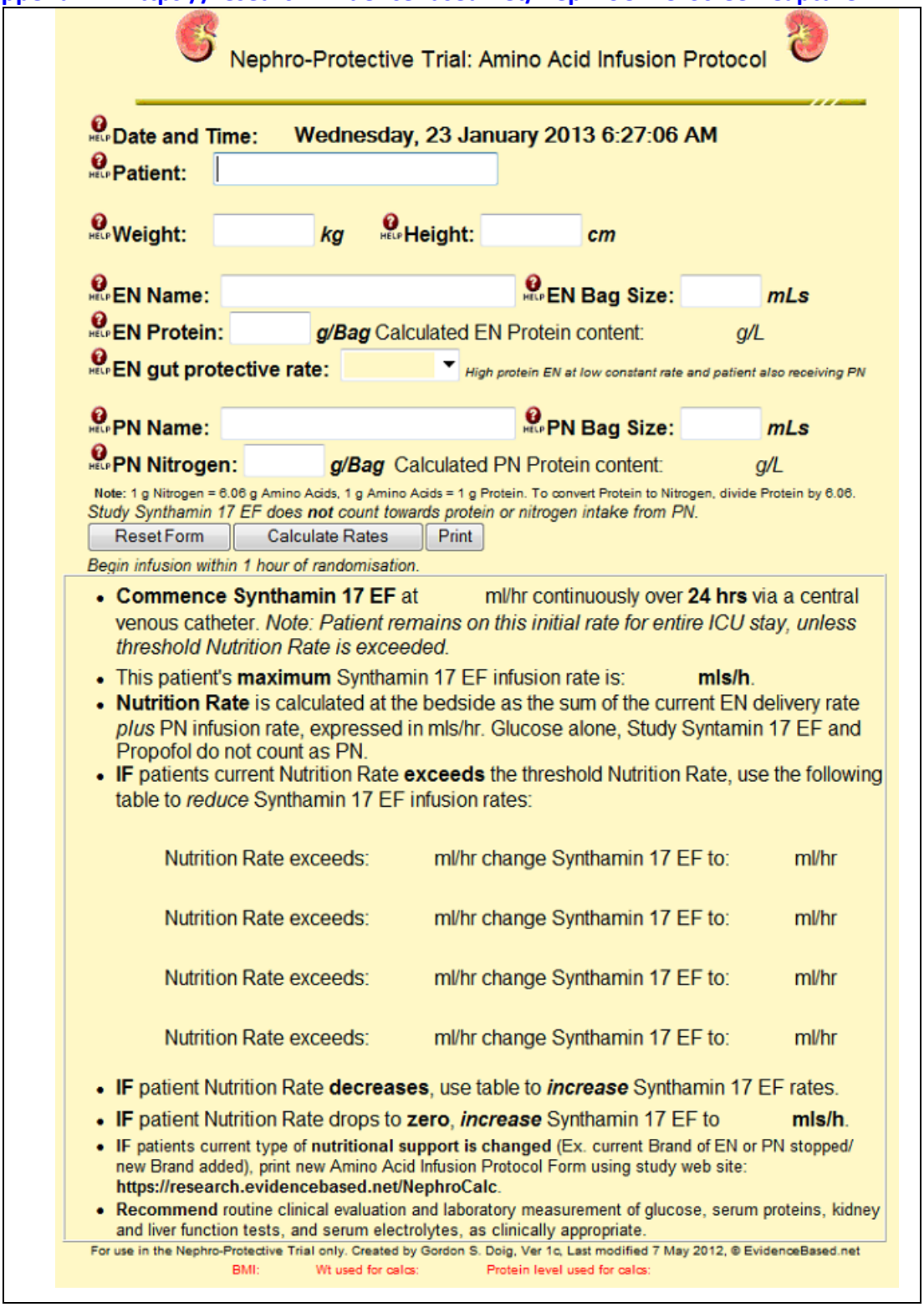


Standard Care						
N = 234	220	198	170	148	133	120
Amino acid supplement						
N = 238	231	210	182	160	141	124

Patients in ICU at end of each study day

ICU: Intensive Care Unit; Error bars indicate 95% confidence intervals around differences between groups.

eAppendix 1: https://research.EvidenceBased.net/NephroCALC Screen Capture



Nephro-Protective Trial: Amino Acid Infusion Protocol

Date and Time: Wednesday, 23 January 2013 6:27:06 AM

Patient:

Weight: kg Height: cm

EN Name: EN Bag Size: mLs

EN Protein: g/Bag Calculated EN Protein content: g/L

EN gut protective rate: *High protein EN at low constant rate and patient also receiving PN*

PN Name: PN Bag Size: mLs

PN Nitrogen: g/Bag Calculated PN Protein content: g/L

Note: 1 g Nitrogen = 6.06 g Amino Acids, 1 g Amino Acids = 1 g Protein. To convert Protein to Nitrogen, divide Protein by 6.06.

*Study Synthamin 17 EF does **not** count towards protein or nitrogen intake from PN.*

Reset Form | Calculate Rates | Print

Begin infusion within 1 hour of randomisation.

- **Commence Synthamin 17 EF** at ml/hr continuously over **24 hrs** via a central venous catheter. *Note: Patient remains on this initial rate for entire ICU stay, unless threshold Nutrition Rate is exceeded.*
- This patient's **maximum** Synthamin 17 EF infusion rate is: **mls/h**.
- **Nutrition Rate** is calculated at the bedside as the sum of the current EN delivery rate *plus* PN infusion rate, expressed in mls/hr. Glucose alone, Study Syntamin 17 EF and Propofol do not count as PN.
- **IF** patients current Nutrition Rate **exceeds** the threshold Nutrition Rate, use the following table to *reduce* Synthamin 17 EF infusion rates:

Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr

- **IF** patient Nutrition Rate **decreases**, use table to ***increase*** Synthamin 17 EF rates.
- **IF** patient Nutrition Rate drops to **zero**, ***increase*** Synthamin 17 EF to **mls/h**.
- **IF** patients current type of **nutritional support is changed** (Ex. current Brand of EN or PN stopped/ new Brand added), print new Amino Acid Infusion Protocol Form using study web site: **https://research.evidencebased.net/NephroCalc**.
- **Recommend** routine clinical evaluation and laboratory measurement of glucose, serum proteins, kidney and liver function tests, and serum electrolytes, as clinically appropriate.

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BMI: Wt used for calcs: Protein level used for calcs: