Nutrition and Nephro-Protection: Creatinine, much ado about nothing?

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www.EvidenceBased.net

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Outline

• Brief context and background to the Nephro-Protective Trial

• Key elements of design

• Present measures of kidney function

• Discuss reliability of measures of kidney function in critical illness
Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults
A Cluster Randomized Controlled Trial

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Geoff Dobb, FFICM
for the Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group

Context Evidence demonstrates that providing nutritional support to intensive care unit (ICU) patients within 24 hours of ICU admission reduces mortality. However, early feeding is not universally practised. Changing practice in complex multidisciplinary environments is difficult. Evidence supporting whether guidelines can improve ICU feeding practices and patient outcomes is contradictory.

Objective To determine whether evidence-based feeding guidelines, implemented using a multifaceted practice change strategy, improve feeding practices and reduce mortality in ICU patients.

Design, Setting, and Patients Cluster randomized trial in ICUs of 27 community and tertiary hospitals in Australia and New Zealand. Between November 2003 and May 2004, 1,118 critically ill adult patients expected to remain in the ICU longer than 2 days were enrolled. All participants completed the study.

Interventions Intensive care units were randomly assigned to guideline or control groups. Guideline ICUs developed an evidence-based guideline using Brownson’s Clinical Practice Guideline Development Cycle. A practice-change strategy composed of 18 specific interventions, leveraged by educational outreach visits, was implemented in guideline ICUs.

Main Outcome Measures Hospital discharge mortality. Secondary outcomes included ICU and hospital length of stay, organ dysfunction, and feeding process measures.

Results Guideline and control ICUs enrolled 561 and 557 patients, respectively. Guideline ICUs fed patients earlier (0.75 vs 1.37 mean days to enteral nutrition start; difference, −0.62 [95% confidence interval (CI), −0.82 to −0.36]; P < 0.001 and 1.04 vs 1.40 mean days to parenteral nutrition start; difference, −0.35 [95% CI, −0.61 to −0.09]; P = 0.04) and achieved caloric goals more often (6.0 vs 5.02 mean days per 10 fed patient-days; difference, 1.07 [95% CI, 0.12 to 2.22]; P = 0.03). Guideline and control ICUs did not differ with regard to hospital discharge mortality (28.9% vs 27.4%; difference, 1.4% [95% CI, −6.3% to 12.0%]; P = 0.70) or to hospital length of stay (24.2 vs 24.3 days; difference, −0.06 [95% CI, −0.38 to 0.44]; P = 0.97) or ICU length of stay (9.1 vs 9.9 days; difference, −0.86 [95% CI, −2.6 to 1.3]; P = 0.42).

Conclusions Using a multifaceted practice change strategy, ICUs successfully developed and implemented an evidence-based nutritional support guideline that promoted earlier feeding and greater nutritional adequacy. However, use of the guideline did not improve clinical outcomes.

Trial Registration anzctr.org.au Identifier: ACTRN12608000407392

Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults: A Cluster Randomized Controlled Trial

Reduction in AKI

<table>
<thead>
<tr>
<th>Table 4. Clinically Significant Organ Dysfunction</th>
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<tbody>
<tr>
<td>Mean Organ System Failures</td>
<td>Guideline (14 ICUs, 561 Patients)</td>
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<tr>
<td>Renal (creatinine &gt;1.923 mg/dL), dysfunction days/10 patient-days</td>
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<td>Organ system dysfunctions, No./patient-day</td>
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Hypothesis generating sub-group analysis:

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Patients at high risk of AKI at study entry:

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Out of 1,118 patients enrolled, 242 high risk patients were identified.

- Duration of AKI was shorter in high risk patients randomized to be fed according to the Guideline (3.8 vs 5.6 AKI days per 10 day stay, p=0.009).

- Significantly fewer Guideline-fed high risk patients received dialysis whilst in ICU (33% vs 46%, p=0.028).


Renal function and protein intake

In the healthy adult, renal blood flow and glomerular filtration rate (GFR) increase by **25 to 60%** for several hours after the consumption of a high protein meal or IV infusion of L-amino acids.

Landmark RCT: AKI and protein intake

Equipoise for a Phase II clinical trial

A Phase II clinical trial:

- Establishes the *efficacy* of a drug, against a placebo or standard care, using surrogate, physiological or biochemical endpoints.
- Generates *safety* information.

www.evidencebased.net/NephroProtect
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Hypothesis:

In critically ill patients, who are at risk of developing acute kidney injury (AKI), does *more consistent* and *higher* protein intake *prevent the onset*, *reduce the severity* and *enhance recovery from* clinically significant renal dysfunction?

www.evidencebased.net/NephroProtect
To ensure *more consistent* and *higher* protein intake, patients received a supplementary infusion of standard *electrolyte free* Amino Acid solution (Synthamin 17 EF, Baxter Healthcare, Australia):

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1) Patients not receiving EN or PN
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2) Patients receiving EN or PN
   - Synthamin 17 EF infusion was titrated to achieve target intake of 2.0 g protein/amino acids per Kg.
Pragmatic Standard Care

- The attending clinician selected the route, starting rate, metabolic targets, measures of tolerance and composition of feeds to be used in standard care patients based on current practice in their ICU.
Eligibility Criteria

Main inclusion criteria:

- Adult patient on their First or Second calendar day of admission to the study ICU.
- Expected to remain in the study ICU at least two more days.

www.evidencebased.net/NephroProtect
Eligibility Criteria

Main inclusion criteria:

- Adult patient on their First or Second calendar day of admission to the study ICU.
- Expected to remain in the study ICU today and tomorrow.

Main exclusion criteria:

- Current Severe Kidney Failure
- History of kidney transplant
- Product licensing contraindication to IV amino acids
Results

Recruitment ran from 2\textsuperscript{nd} December 2010 to 26\textsuperscript{th} February 2013.

- 16 participating hospitals throughout Australia and New Zealand.
- 474 patients were enrolled and randomised
  - 235 randomised to standard care
  - 239 randomised to Nephro-Protect

\textit{All enrolled patients were included in the primary analysis.}
### Demographics

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<td>88 (37.5)</td>
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<td>ICU discharge mortality, % (n/N)</td>
<td>12.8% 30/235</td>
<td>11.7% 28/239</td>
<td>0.78</td>
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<td>Hospital discharge mortality, % (n/N)</td>
<td>18.3% 43/235</td>
<td>15.5% 37/239</td>
<td>0.46</td>
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</table>
Nutrition therapy process measures

B

Protein delivered per study day (all patients)

239 High Protein patients
235 Standard Care patients

g/kg (lbw used if BMI > 25)

Days in ICU after study enrolment

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Energy delivered per patient (all patients, not including study Synth)

- **239 High Protein patients**
- **235 Standard Care patients**
Measures of kidney function

Creatinine

- Assayed using Jaffe Method, on the Abbott Architect chemistry analyser
- measured daily in ICU patients
- 2 to 5 cents per assay
Measures of kidney function

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Cystatin C
- A novel measure of renal function that may provide more accurate estimates of GFR than creatinine
- produced at a stable rate by all nucleated cells
- Assayed using Particle Enhanced Tubidometric Immuno Assay (PETIA), on the Abbot Architect chemistry analyser
- $16 per assay
- ‘skip pattern’ used to maximise information gain and minimise costs
  - Sampled at study baseline and study Day 1, 3, 5, 7, 10, 13, 16
CKD-EPI eGFR, Creatinine

![Graph showing eGFR from Creatinine by Study Day]

- **Creatinine**: 239 High Protein patients
- **Creatinine**: 235 Standard care patients

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**CKD-EPI eGFR, Creatinine**

- Fully factorial repeated measures ANOVA: $p = 0.004$ for treatment x time interaction
- Early peak difference of 7.7 mls/min/1.73m$^2$ on Day 4

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**CKD-EPI eGFR, Cystatin C**

Estimated Glomerular Filtration Rate (CKD-EPI) by Study Day, 474 Critically Ill Patients

- **Cystatin C**
  - 239 High Protein patients
  - 235 Standard care patients

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- Fully factorial repeated measures ANOVA: $p = 0.097$ for treatment $\times$ time interaction
- Early peak difference of 5.4 mls/min/1.73m$^2$ on Day 7
Renal function: CysC vs Creatinine

- Meta-analysis of 54 articles with 4,492 patients.
- CysC eGFR and creatinine eGFR compared to a ‘gold standard’ measurement of GFR: inulin, $^{51}$Cr-EDTA, $^{99}$Tm-DTPA, iothalamate($^{125}$I), or iohexol.

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- CysC eGFR and creatinine eGFR compared to a ‘gold standard’ measurement of GFR: inulin, $^{51}$Cr-EDTA, $^{99}$Tm-DTPA, iothalamate($^{125}$I), or iohexol

- aROC Cystatin C = 0.926 (95% CI, 0.892 to 0.960)
- aROC Creatinine = 0.837 (95% CI, 0.796 to 0.878)

$P < 0.001$


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Renal function: CysC vs Creatinine

- 47 ICU patients
- CysC eGFR and creatinine eGFR compared to the ‘gold standard’ iohexol GFR


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Renal function: CysC vs Creatinine

- 47 ICU patients
- CysC eGFR and creatinine eGFR compared to the ‘gold standard’ iohexol GFR
  - aROC Cystatin C = 0.942
  - aROC Creatinine = 0.799
  - $P < 0.014$

CysC and Creatinine over time

Original Articles

Impact of sepsis on levels of plasma cystatin C in AKI and non-AKI patients

Johan Mårtensson, Claes-Roland Martling, Anders Oldner and Max Bell

• 327 ICU patients with sepsis, AKI, sepsis + AKI or neither


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CysC and Creatinine over time

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Daily creatinine and cystatin C measurements over first week of ICU stay


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• Change in cystatin C did not depend on presence of AKI or sepsis


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Cystatin C change (from baseline)


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CysC and Creatinine over time


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Creatinine, Creatine and Phosphocreatine

• **Creatinine** is an ‘end-metabolite’ of the **creatine phosphokinase reaction** (CPK)


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Creatinine is an ‘end-metabolite’ of the creatine phosphokinase reaction (CPK).

CPK is an enzyme that catalyses creatine to the high-energy form, phosphocreatine (consuming ATP).
Creatinine, Creatine and Phosphocreatine

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    - It is an ideal energy storage molecule and it can shuttle energy between areas where ATP is produced and areas where ATP is used

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    • It is an ideal energy storage molecule and it can shuttle energy between areas where ATP is produced and areas where ATP is used
    • Found in high concentrations in the heart, skeletal muscles (90% of total body creatine), spermatozoa and photoreceptor cells of the retina
  • After 30-60 seconds of strenuous exercise, we deplete phosphocreatine stores, which are replenished over the next 5 - 20 minutes

Creatine Phosphokinase Reaction


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Creatine Phosphokinase Reaction

- Creatinine is an ‘end-metabolite’ produced when creatine and phosphocreatine degrade by hydrolyses.
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What would happen if the reaction shifts ‘right’ in critical illness?

Survival in Critical Illness Is Associated with Early Activation of Mitochondrial Biogenesis

Jane E. Carré¹, Jean-Christophe Orban¹², Lorenza Re¹³, Karen Felsmann⁴, Wiebke Iffert⁴, Michael Bauer⁵, Hagir B. Suliman⁶, Claude A. Plantadosi⁶, Terry M. Mayhew⁷, Patrick Breen¹, Martin Stotz¹, and Mervyn Singer¹

• Muscle biopsies from 16 ICU patients, 10 age-matched controls

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- Muscle biopsies from 16 ICU patients, 10 age-matched controls

“skeletal muscle mitochondrial capacity was decreased soon after intensive care admission”
CPK Reaction Shifts Right In Critical Illness

- About 5:1 PCr:Cr ratio in Controls (83% phosphocreatine)

CPK Reaction Shifts Right In Critical Illness

- About 5:1 PCr:Cr ratio in Controls (83% phosphocreatine)
- About 2:1 PCr:Cr ratio in Survivors (66% phosphocreatine)

CPK Reaction Shifts Right In Critical Illness

• About 5:1 PCr:Cr ratio in Controls (83% phosphocreatine)
• About 2:1 PCr:Cr ratio in Survivors (66% phosphocreatine)
• About 4:1 PCr:Cr ratio in non-survivors (80% phosphocreatine)

• About 5:1 PCr:Cr ratio in Controls (83% phosphocreatine)
• About 2:1 PCr:Cr ratio in Survivors (66% phosphocreatine)
• About 4:1 PCr:Cr ratio in non-survivors (80% phosphocreatine)

CPK Reaction Shifts Right In Critical Illness

Longitudinal Changes of Biochemical Parameters in Muscle During Critical Illness

Lena Gamrin, Kerstin Andersson, Eric Hultman, Eva Nilsson, Pia Essén, and Jan Wernerman

• 9 ICU patients (trauma, major surgery, sepsis)
• 2 muscle biopsies obtained (1st 3–11 days after ICU admit, 2nd 3–7 days later)


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### Table 5. Skeletal Muscle Energy-Rich Phosphates in Critically Ill Patients Investigated With Repeated Sampling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Unit</th>
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<th>Biopsy 2</th>
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CPK Reaction Shifts Right In Critical Illness

Table 5. Skeletal Muscle Energy-Rich Phosphates in Critically Ill Patients Investigated With Repeated Sampling

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![Diagram showing the metabolism of creatinine, creatine, and phosphocreatine.]

70% 30%

- 2.6% of PCr reserves per day
- 1.1% of creatine reserves per day


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20% reduction in production of creatinine over 3 to 7 days of critical illness??

Rats (n=5 per group) randomised to bilateral nephrectomy or bilateral nephrectomy + sepsis (cecal ligation and perforation)

Reduced Production of Creatinine Limits Its Use as Marker of Kidney Injury in Sepsis

Kent Doi, Peter S.T. Yuen, Christoph Eisner, Xuzhen Hu, Asada Leelahavanichkul, Jürgen Schnerrmann, and Robert A. Star

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

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- Creatinine levels obtained 18 h after initial surgery

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Bilateral nephrectomy removes creatinine elimination from the equation
  - 18 h creatinine levels depend only on creatinine production.

CPK Reaction Shifts Right In Critical Illness

Creatinine, 18 h after surgery


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Significantly lower creatinine production in septic rats.

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  • muscle biopsies of ICU patients provide pathophysiological rationale and animal models provide additional evidence of decreased production

Continued use of creatinine to assess renal function in critical illness may hamper clinical decision making and compromise patient outcomes
Congratulations and sincere thanks to everyone who contributed towards making this trial a success!!!

**Site Investigators:** Sharon Allsop, Irene Bailey, Marilyn Beggs, Rinaldo Bellomo, Allison Bone, John Botha, Jodi Brown, Rob Cameron, Paul Carless, Claire Cattigan, Michael Davis, Graeme Duke, Emily Dynon, Glenn Eastwood, Tania Elderkin, Katrina Ellem, Espedito Farone, Melissa Fraser, Kalpesh Gandhi, Wenli Geng, Eileen Gilder, Tanya Gilliver, Rebecca Gresham, Sachin Gupta, Miranda Hardie, Peter Harrigan, Gwen Hickey, Liz Hickson, Chantal Hogan, Jenny Holmes, Deborah Inskip, Theresa Jacques, Bronwyn Johnson, Serena Knowles, David Lewis, Deirdre Mathai, Kirilee Matters, Lianne McCarthy, Shay McGuiness, Priya Nair, Kiran Nand, Maria Nikas, Neil Orford, Phoebe Palejs, Rachael Parke, Leah Peck, Emma Pollock, Alan Rashid, Michael Reade, Claire Reynolds, Anne Ritchie, Laura Rust, Tania Salerno, John Santamaria, Treena Sara, Ian Seppelt, Rebecca Sidoli, Roger Smith, Rima Song, Martin Sterba, Karen Storer, Amy Sutherland, Judy Tai, Anna Tilsley, Leonie Weisbrodt, Sarah Whereat, Anna Whitley, Tony Williams and Helen Young.

**Management Committee:** Gordon Doig, Fiona Simpson, Elizabeth Sweetman, Phillipa Heighes, Doug Chesher, Rinaldo Bellomo, Carol Pollock, Andrew Davies, Michael Reade, Peter Harrigan, Prasad Devarajan and John Botha.

www.evidencebased.net/NephroProtect
Measures of kidney function

GFR Calculators: Serum Creatinine and Cystatin C (2012) (With SI Units)


programmed by Stephen Z. Fadem, M.D., FACP, FASN and Brian Rosenthal

Serum creatinine

mg/dL, µmol/L

Serum Cystatin C (mg/L)

NOTE: CKD-EPI GFR is only valid with serum creatinine methods are traceable to IDMS

Age

years

Race

* African American  © All other races

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Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure

Katarina Fredriksson, Folke Hammarqvist, Karin Strigård, Kjell Hultenby, Olle Ljungqvist, Jan Wernerman, and Olav Rooyackers.

• Muscle biopsies from 10 ICU patients with sepsis and MODS, 10 age-matched controls
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“Concentrations of ATP and phosphocreatine were, respectively, 40 and 34% lower, and lactate concentrations were 43% higher in leg muscle.”


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53 adult critically ill patients with severe ARF requiring dialysis randomised to receive:

1) Glucose infusion or
   • 1,296 kcals/day progressing to 3,240 kcals/day

2) Glucose infusion plus amino acids
   • Glucose as above plus
   • 13 g/day progressing to 26 g/day

Results:

• Patients receiving AA’s recovered from ARF faster
  • rate of creatinine decrease, p=0.03
• Patients receiving AA’s had a significantly higher survival rate
  • 44% (11/25) vs 75% (21/28), p=0.02