The *REDOXS*©–Study
REducing Deaths due to OXidative Stress

Algorithm for Elevated Urea in Patients with Renal Disease

1. **I am about to start the study supplements in a patient with existing renal dysfunction (elevated Creatinine, either acutely or chronically, particularly if they meet the criteria for renal dysfunction listed on the inclusion criteria, is there anything special I should do?**

   Response: The study solutions contain trivial amounts of K+ but do contain above average amounts of protein (the protein composition could range from 0-90 gms of protein/day) and will require 750 ml/day of fluid to administer the study nutrients. Therefore, at the outset of starting the study supplements in patients with renal dysfunction, we recommend you concentrate all IV infusions and use concentrated, lower protein enteral feeding products, like Nepro, Suplena, Novasource Renal, etc. If after the first few days there are no significant elevations in urea or fluid concerns, you may consider switching to a standard enteral formula.

2. **In patients with pre-existing renal dysfunction (either acute or chronic that receive study supplements containing high dose glutamine, the urea may rise disproportionately to the serum Creatinine. The patient does not have a standard indication for dialysis. How safe is this and what should be done about it?**

   Response: We know the following:

   i. Glutamine is associated with a potential survival benefit in critically ill patients (1).
   ii. Doses of glutamine similar to or higher than what we are prescribing in this study are described as "safe and well tolerated" (2,3). The observed benefits of glutamine are observed in patients despite high urea levels (4).
   iii. High dose glutamine is associated with no worsening of renal function or SOFA scores (composite organ function) and lower levels of markers of oxidative stress (preliminary results of dosing study).
   iv. High dose glutamine and antioxidants were associated with greater resolution of SOFA scores compared to standard feeds (5).
   v. In the acute setting, high protein loads are NOT harmful to kidney function whereas they may be in patients with chronic renal failure.
   vi. High levels of blood urea in patients with advanced renal failure have been shown to be safe and non-toxic if less than 107 mmol/L (6).

   To underscore an important point, this discussion only applies to patients who are not receiving or about to receive dialysis. In other words, if the urea is elevated and the patient does not meet standard criteria for dialysis. This problem has been discussed extensively at the Canadian Critical Care Trials Group and with study investigators with input from our nephrology colleagues.

We are relatively certain that the disproportionately elevated urea in the setting of a study patient with renal dysfunction (acute or chronic) does not represent a safely hazard and we encourage the use of study nutrients in patients with a high urea. Remember, all serious adverse events in study patients will be reviewed by a third party data safety monitoring committee.

If the patient is NOT going to be dialyzed and you are comfortable with the high urea level, continue with both the enteral and parenteral study supplements.

If the clinicians at the bedside are uncomfortable with the high urea, we want to provide them the option to withhold study supplements but in an attempt to standardize the response across the sites, we recommend the following approach:

If the patient is not going to be dialyzed (as they have not reached the standard criteria for dialysis) **and** if the urea ≥ 50 mmol/L, AND the clinician caring for the patient is uncomfortable with the high urea, we suggest the following approach:

1. **Use lower protein enteral products** to minimize protein load and check urea the next day. If urea still remains ≥ 50 mmol/L, proceed to step # 2.
2. **Withhold the enteral feeds for one day**. There is no evidence that withholding calories for a few days will have a negative impact in the course of a long-term ICU patient. In fact, current evidence would support the notion of restrictive or hypocaloric feeding (7). If urea drops below 45 mmol/L on subsequent days, you may resume enteral feeds. If urea still remains ≥ 50 mmol/L, proceed to step # 3.
3. **Reduce the enteral study supplement by one-half the rate, from 20 ml/hr to 10 ml/hr for 24 hours and then reassess.** If urea drops below 45 mmol/L on subsequent days, resume enteral study solution at full rate (20 ml/hr). If urea still remains ≥ 50 mmol/L, proceed to step # 4.
4. **Advise the study pharmacist (who is unblinded) to withhold half the glutamine dose (if the patient is receiving glutamine) in the parenteral study supplements. It is important that the study coordinator and site PI remain blinded. Do not ask if the patient is receiving glutamine.** If urea drops below 45 mmol/L on subsequent days, notify study pharmacist to resume full dose parenteral glutamine. If urea still remains ≥ 50 mmol/L, proceed to step # 5.
5. **Advise the study pharmacist (who is unblinded) to withhold ALL the glutamine dose (if the patient is receiving glutamine) in the parenteral study supplements.** If urea drops below 45 mmol/L on subsequent days, notify study pharmacist to resume full dose parenteral glutamine. If urea still remains ≥ 50 mmol/L, proceed to step # 6.
6. **Discontinue the enteral study supplement for 24 hours and then reassess.** If urea drops below 45 mmol/L on subsequent days, resume enteral study solution at full rate (20 ml/hr). If urea still remains ≥ 50 mmol/L, proceed to step # 7.

7. Start dialysis when clinically indicated and resume both enteral and parenteral study supplements. Reassess urea levels daily.

NOTE: If at any point, enteral feeds or study supplements are withheld, the urea falls, the feeds/supplements are resumed, and the urea rises to > 50 mmol/L again, go to the beginning of the algorithm and start with step #1.

At any point through this algorithm, if a patient receives dialysis, return to full dose parenteral and enteral study supplements.

3. **Patients receiving both parenteral and enteral study solutions will receive approximately 750 ml/day. In patients with volume overload concerns, this may be too much fluid, can we reduce the amount or stop the study solutions?**

   Response:

   If at all possible, please **do not** stop study supplements for volume management of study patients. The solutions are as concentrated as they can be already. If you are concerned about excessive fluid we suggest the following in the order listed below:

   1. Restrict other fluids the patient is receiving and switch to a concentrated feeding formula (2cal/ml).

   2. Consider using diuretics to achieve negative fluid balance.

   3. If still unsuccessful with fluid management and in critical situations, consider dialysis. You may reduce the enteral study supplements to 10 ml/hr for one day to see if that helps but continue with the parenteral study supplements. Resume full rate of enteral study supplements as soon as possible.

NOTE: Withholding the enteral and parenteral study supplements may result in a protocol violation (on any given study day, patient receives less than 80% of prescribed enteral study nutrients or less than 90% prescribed parenteral study nutrients). {Refer to section on Protocol Violation}.

Inclusion criteria for Renal Dysfunction

In patients without known renal disease, renal dysfunction is defined as:

- a serum creatinine ≥171 μmol/L or
- a urine output of less than 500 ml/last 24 hours (or 80 ml/last 4 hours if a 24 hour period of observation is not available).

In patients with chronic renal failure, renal dysfunction is defined as:

- an absolute increase of ≥80 μmol/L from baseline or pre-admission creatinine or
- a urine output of less than 500 ml/last 24 hours (or 80 ml/last 4 hours).

References

1.Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002 Sep;30(9):2022-9

2.Ward E, Picton S, Reid U, Thomas D, Gardener C, Smith M, Henderson M, Holden V, Kinsey S, Lewis I, Allgar V. Oral glutamine in paediatric oncology patients: a dose finding study. Eur J Clin Nutr. 2003 Jan;57(1):31-6.

3. Tjader I, Rooyackers O, Forsberg AM, Vesali RF, Garlick PJ, Wernerman J. Effects on skeletal muscle of intravenous glutamine supplementation to ICU patients. Intensive Care Med. 2004 Feb;30(2):266-75

4. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. Crit Care Med. 2001 Nov;29(11):2075-80

5.Beale R, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, Neilson A, Schneider H. Early enteral supplementation with pharmaconutrients in critically ill patients. Crit Care Med 2004;32: A4.

6.Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW. Effects of urea loading in patients with far-advanced renal failure. Mayo Clinic Proceedings 1972;47:21-29.

7.Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest. 2003 Jul;124(1):297-305.