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

A randomized trial of glutamine and antioxidant supplementation in critically ill patients

Dietitian Manual

This study is registered at Clinicaltrials.gov.
Identification number NCT00133978

September 21st, 2007

Table of Contents

Study Contacts

- **Principal Investigator**

Dr Daren Heyland
Kingston General Hospital
Angada 4, 76 Stuart Street
Kingston ON K7L 2V7
Tel: 613-549-6666 ext. 3339
Fax: 613-548-2428
Email: dkh2@ queensu.ca

- **Project Leader**

Rupinder Dhaliwal, RD
Kingston General Hospital
Angada 4, 76 Stuart Street
Kingston ON K7L 2V7
Phone 613-549-6666 ext 3830
Cell Phone: 613-484-3830
Fax: 613-548-2428
Email dhaliwar@kgh.kari.net

Dietitian Responsibilities

The ICU dietitian at each participating site will ensure that the patients enrolled to the REDOXS© study receive adequate enteral nutrition (or parenteral nutrition if enteral route is contra-indicated) as recommended by the Canadian Clinical Practice Guidelines for Nutrition Support (Heyland, Dhaliwal, Drover et al JPEN 2003. For updated versions, refer to www.criticalcarenutrition.com).

The dietitian will also assist the Study Coordinator in collecting data on the delivery of nutrition in these patients.

The dietitian will work in collaboration with the STUDY COORDINATOR to minimize the interruptions to the study supplements.

Please refer to the **"Administration of Study Supplements Manual",** for details on the study supplements.

Study Duration

The study period is from ICU admission until day 30 unless ICU discharge (actual) or death occurs before day 30. All daily data collection including the data on enteral and parenteral nutrition will continue for this duration unless enteral or parenteral nutrition has been discontinued permanently and the patient has progressed to oral intake before day 30.

The study supplements will be provided for a maximum of **28 days** from randomization, unless ICU discharge/death occurs before this. Data collection pertaining to the study supplements will continue for this duration.

THE DURATION OF THE STUDY SUPPLEMENTS SHOULD NOT EXCEED A TOTAL OF 28 DAYS.
Study supplements will be discontinued in the event that the patient is discharged from ICU or dies before 28 days (exception: patients with ICU stay < 5 days and transferred to ward; duration of study supplements should be 5 days in total = 120 hours).

Data Collection

The collection of nutrition data will assist the dietitian in determining whether the REDOXS© patients are being fed adequately via enteral (or parenteral nutrition). The data may be collected retrospectively, however collecting data on a daily basis will allow the dietitian to identify and resolve gaps in current practice in a timely manner.

The dietitian will not be entering any data in to the web based data capture system, but will be providing the data to the Study Coordinator who is responsible for entering the data. Web shots are shown here to illustrate the type of data that needs to be collected.

It is recommended that the dietitian work closely with the Study Coordinator to determine the best approach for collecting the data (worksheets/daily checklists, etc). A sample check list is provided (see page 18).

Baseline Nutrition

Prescribed Energy and Protein Intake
This will need to be calculated by the dietitian once at baseline as below:

- The prescribed energy and protein intake is the kilocalories and grams of protein provided by the goal regimen (i.e. maximum rate/volume determined at the initial assessment) for EN/PN according to the dietitian's recommendation.
    - For eg. If the dietitian recommends a starting rate of 25 ml/hr on day 1 with a final rate of 75 ml/hr by day 3, calculate the calories and protein that the final rate = 75ml/hr X 24 would provide.

- Include calories from protein.

- If the patient is on enteral nutrition and parenteral nutrition at the same time, the prescribed energy and protein intake will still be the FINAL amount as assessed by the dietitian.

- **If the prescription changes over the days of observation, calculate the average prescribed calories and protein.**

Enteral Nutrition/Parenteral Nutrition Start and Stop Dates
The Study Coordinator is responsible for collecting this data but the dietitian is encouraged to work with the Study Coordinator to determine the best approach for collecting this data.

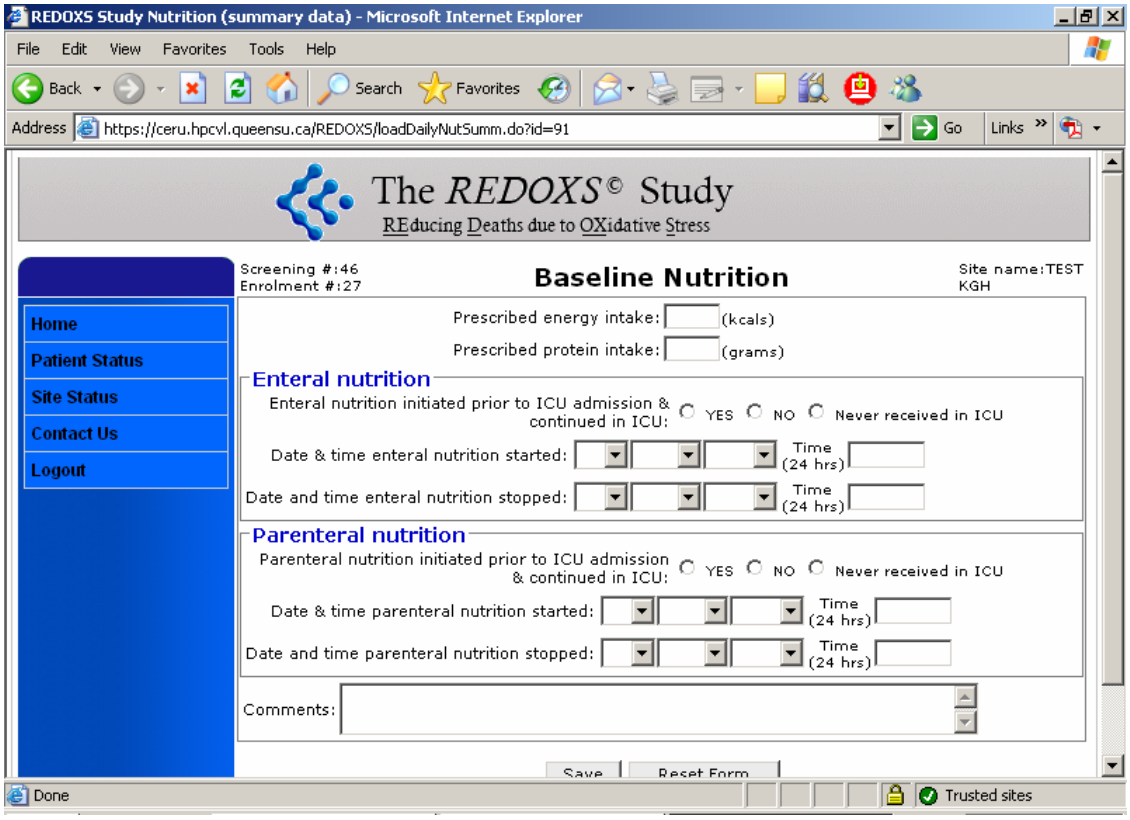
Enteral Nutrition
- Indicate if enteral nutrition was started prior to ICU admission and continued in ICU, "Yes" or "No" or whether it was never received in ICU.
    - If Yes, use ICU admission date/time as enteral nutrition start date/time.
    - If No, record the date and time enteral nutrition was started in ICU.

- Record the date and time that enteral nutrition was discontinued (permanently) in ICU.
    - If enteral nutrition is continued beyond ICU discharge, record the ICU discharge as the date and time enteral nutrition was stopped even if the study supplements are continued beyond ICU discharge (in patients that are in ICU < 5 days).

Parenteral Nutrition

- Indicate if parenteral nutrition was started prior to ICU admission and continued in ICU, "Yes" or "No" or whether it was never received in ICU.
    - If Yes, use ICU admission date/time as parenteral nutrition start date/time.
    - If No, record the date and time parenteral nutrition was started in ICU.
- Record the date and time that parenteral nutrition was discontinued (permanently) in ICU.
    - If parenteral nutrition is continued beyond ICU discharge, record the ICU discharge as the date and time enteral nutrition was stopped even if the study supplements are continued beyond ICU discharge (in patients that are in ICU < 5 days).

Webshot of Baseline Nutrition



Daily Nutrition Data

This page is for recording daily data pertaining to the delivery of enteral or parenteral nutrition and is separate from the *Study Supplement Forms*.

The data collection for the delivery of enteral and parenteral nutrition is from study Day 1 until study Day 30.
The data collection for the study supplements is from study Day 1 onwards for a maximum of 28 days from randomization.

Study Day 1 is from ICU admission to the end of your 24 hr flowsheet.
Study Day 2 and subsequent days are the 24 hr period according to your flowsheet.

Enteral Nutrition/Parenteral Nutrition

Total Energy Intake

This will need to be calculated by the dietitian daily as follows:

- include calories from protein
- include calories from other supplements.
- include calories from propofol if continuous infusion ≥ 6 hrs. Do NOT include intermittent doses of propofol.
- do **NOT** include calories from IV solutions.
- do **NOT** include calories from the study supplements.

Total Protein Intake

This will need to be calculated by the dietitian daily as follows:

- include protein from supplements.
- do **NOT** include the grams of protein from the study supplements.

- If patient is on a combination of Enteral Nutrition and Parenteral Nutrition, please calculate the calories received from each separately.

If the patient is not receiving enteral or parenteral nutrition but is receiving propofol, you do NOT need to record the calories from propofol.

The dietitian is encouraged to assist the Study Coordinator by collecting the following data.

Type of Enteral Formula

Using the taxonomy on next page, please record enteral formula(s) received.

- If formula not listed on this taxonomy, choose other and write down the name of the formula
- You may record up to 3 formulas per day. In the event that the patient receives more than 3 formulas, record the 3 that provided the largest volumes.

Enteral Nutrition interrupted due to Feeding Intolerance

If patient is on enteral nutrition, indicate Yes or No if enteral nutrition was **ever** interrupted **due to feeding intolerance.**

- An **interruption** in enteral feeding is defined as a reduction in the rate of delivering the feed **or** stopping the feed.
- Feeding **intolerance** is defined as the presence of any one of the following:
    - High gastric residual volumes
    - Emesis
    - Aspiration of enteral nutrition

Enteral Nutrition interrupted due to fluid concerns/elevated urea

If enteral nutrition is interrupted due to high urea or fluids concerns, indicate Yes or No. If yes, provide an explanation.

Formula Taxonomy

	Formula Name
	MEAD JOHNSON: Portagen
	NESTLE: Peptamen with Prebio 1
	NESTLE: Peptamen
	NESTLE: Peptamen 1.5
	NESTLE: Peptamen VHP
	NESTLE: Peptamen AF
	NESTLE: Nutren 2.0
	NESTLE: Nutren 1.5
	NESTLE: Nutren VHP
	NESTLE: Nutren VHP fibre
	NESTLE: Nutren Fibre with Prebio 1
	NESTLE: Nutren Fibre with Prebio 1.5
	NESTLE: Nutrihep
	NESTLE: Supplements - Caloreen
	NOVARTIS: Compleat
	NOVARTIS: Impact
	NOVARTIS: Impact 1.5
	NOVARTIS: Isosource HN
	NOVARTIS: Isosource HN with fibre
	NOVARTIS: Isosource VHN
	NOVARTIS: Isosource 1.5
	NOVARTIS: Novasource Renal
	NOVARTIS: Peptinex
	NOVARTIS: Peptinex DT
	NOVARTIS: Resource 2.0
	NOVARTIS: Resource Plus
	NOVARTIS: Resource Standard
	NOVARTIS: Resource Diabetic
	NOVARTIS: Tolerex
	NOVARTIS: Trauma-cal

	Formula Name
	NOVARTIS: Vivonex TEN
	NOVARTIS: Vivonex Plus
	NOVARTIS: Supplements- Instant Protein Powder
	NOVARTIS: Supplements - Microlipid
	NOVARTIS: Supplements - MCT oil
	NOVARTIS: Supplements-Resource Glutasolve
	ROSS: Jevity 1 kcal
	ROSS: Jevity 1.2 kcal
	ROSS: Osmolite HN Plus
	ROSS: Osmolite HN
	ROSS: Promote
	ROSS: Glucerna
	ROSS: Nepro
	ROSS: Suplena
	ROSS: Pulmocare
	ROSS: Perative
	ROSS: Vital HN
	ROSS: TWO Cal HN
	ROSS: Oxepa
	ROSS: Optimental
	ROSS: Ensure
	ROSS: Ensure High Protein
	ROSS: Ensure Plus
	ROSS: Ensure Fibre
	ROSS: Supplements -Polycose powder
	ROSS: Supplements -Polycose Liquid
	Hormel Health: Immun-Aid
	Hormel Health: Hepatic-Aid
	Other:

Parenteral Lipids

If on parenteral nutrition, indicate with a "Yes" or "No" if patient received lipids.

- If yes, use the taxonomy provided to select the type of lipid (see below).

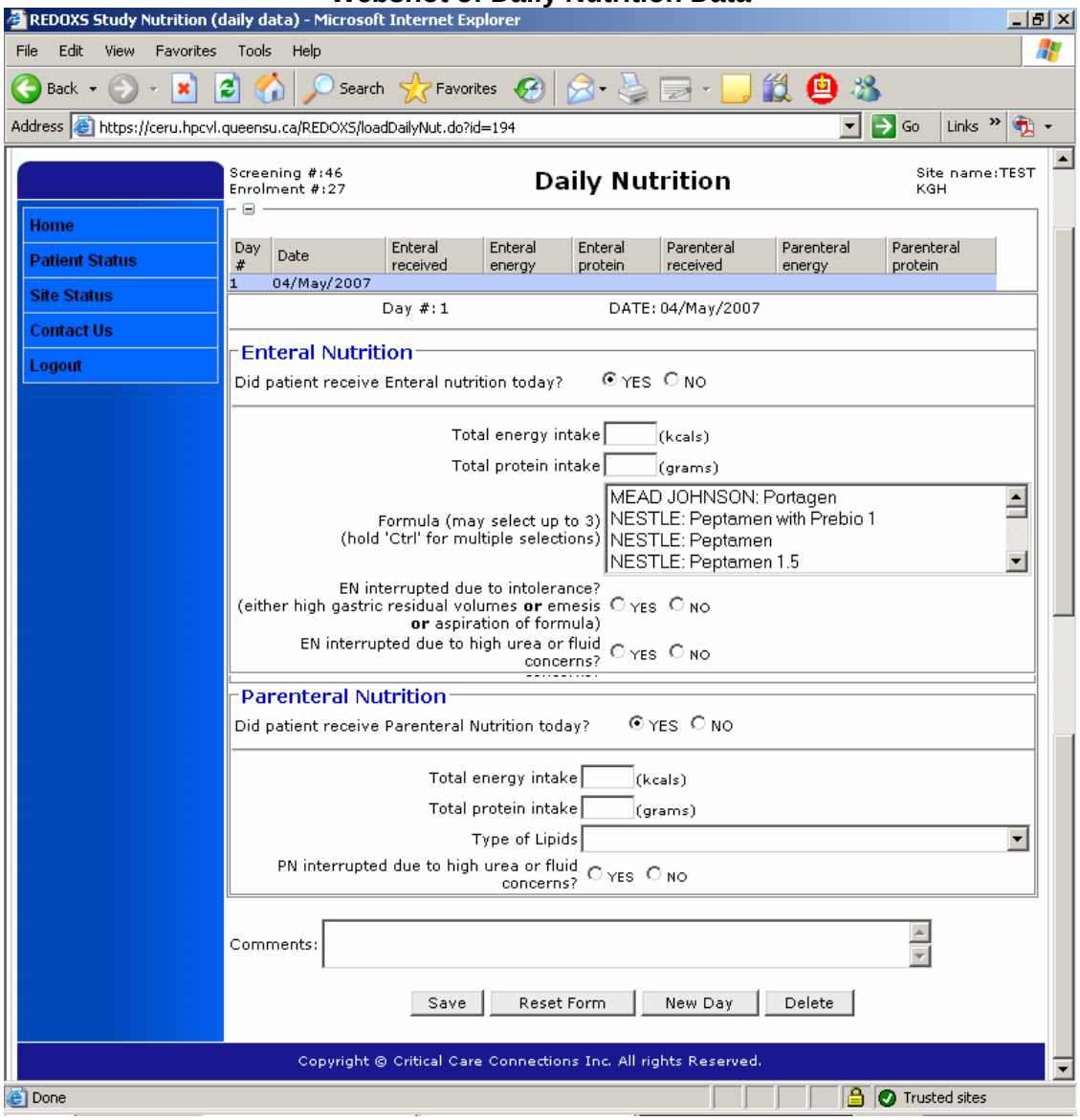
Type of lipids
1. Soybean oil based (LCTs)
2. MCT/LCT physical mixture
3. MCT/LCT structured form
4. Olive Oil based
5. Fish Oil based (10-20% of total lipid emulsion)
6. Mixture of soy oil, MCTs, and fish oil
7. Mixture of soy oil, MCTs, olive oil, and fish oil (SMOF)
8. Other, specify _____

Parenteral Nutrition interrupted due to fluid concerns/elevated urea

If parenteral nutrition is interrupted due to high urea or fluids concerns, indicate Yes or No. If yes, provide an explanation.

The dietitian is to forward all the nutrition related data collected for each REDOXS© patient to the Study Coordinator in a timely manner. The Study Coordinator will enter this this on the web based data capture system.

Webshot of Daily Nutrition Data



Other Vitamins, Minerals, Supplements

Patients that are enrolled in this study should **NOT** to be on enteral formulas, parenteral solutions or supplements that have **elevated** levels of glutamine, antioxidants or selenium, vitamin A,C,E, beta-carotene, zinc or arginine. The patient enrolled in the study should **NOT** be placed on the following:

- Vivonex Plus/T.E.N
- Oxepa
- Optimental
- Impact/Impact 1.5
- Perative
- Peptamen AF
- Probiotics
- Glutamine supplements

The following are exceptions and are allowed:

- Thiamine, folic acid
- Standard multivitamin/mineral preparations (maximum of 5 mg zinc)
- Standard amounts of vitamins and minerals already present in enteral or parenteral solutions (maximum of 5 mg zinc and 60 µgms selenium).
- Vitamin K

In patients on long term parenteral nutrition, supplementation may be necessary and can be started after notifying the Project Leader.

If the patient has been on any of these formulas/supplements prior to enrolment in the study (either at home or in a hospital), these should be discontinued once the patient is enrolled.

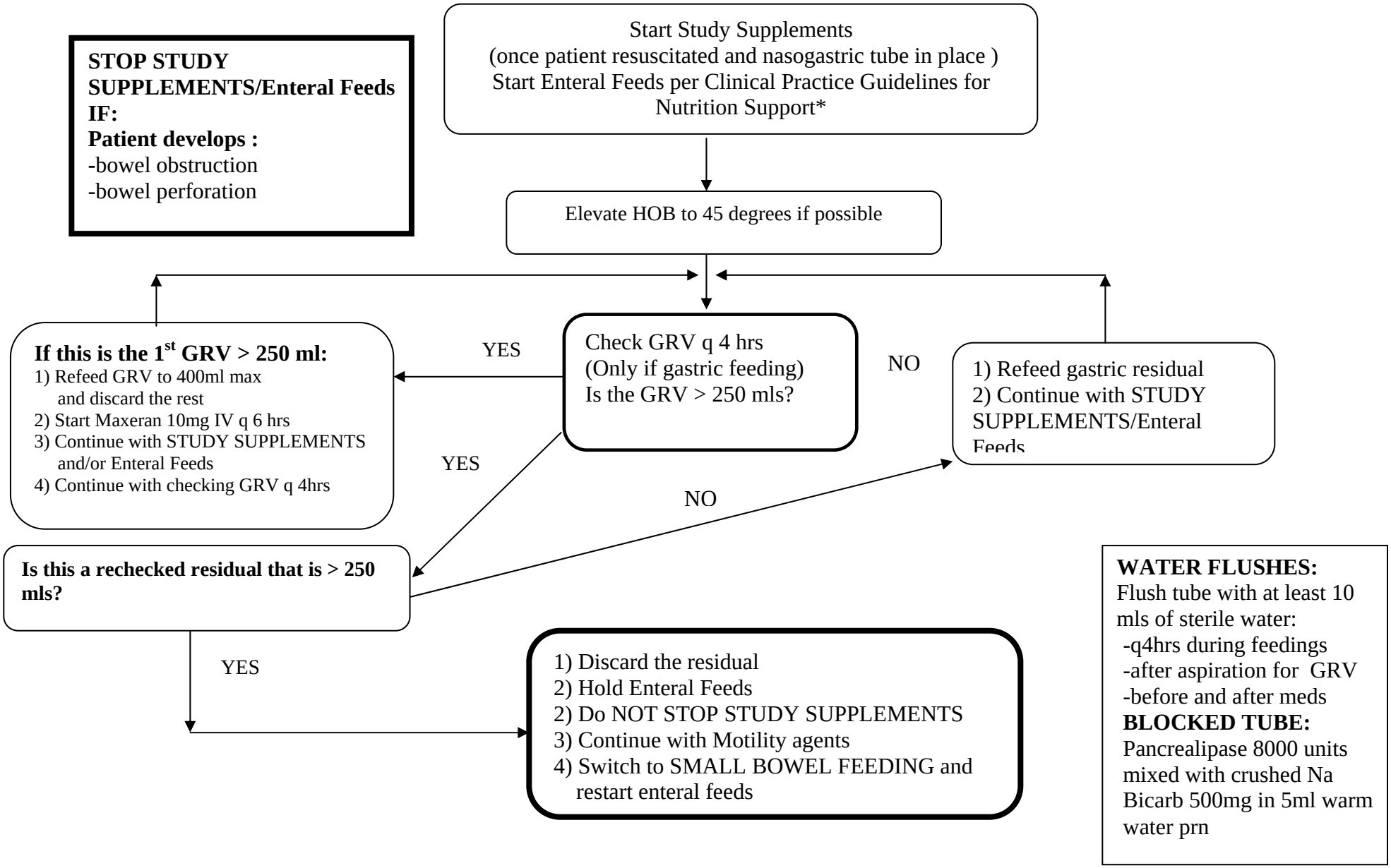
Optimizing Enteral Nutrition and Study Supplements

- To optimize the delivery of enteral nutrition and study supplements in patients enrolled to the REDOXS© study, it is recommended that the following strategies be utilized:
  - Elevate the head of the bed
  - Start motility agents
  - Start small bowel feeding

- Refer to Enteral Feeding Protocol on next page for more details on how to utilize these strategies in a step-wise manner.

- In the event that enteral feeds are poorly tolerated, you may hold the enteral feeds as per your usual practice, however, **DO NOT** stop the study supplements. The study supplements are *nutrients,* and it is safe to deliver these small amounts regardless of whether enteral feeds are tolerated or not.

Enteral Feeding Protocol



* Heyland et al JPEN 27:355-373, 2003

Since the study supplements contain above average amounts of protein (could range from 0-90 gms/day) and require 750 mls fluid/day, decisions about altering the management of the patient with respect to fluid, dialysis, type of enteral (or parenteral) nutrition will need to be made.

If the patient has renal failure, has an elevated urea of concern and is not going to be dialyzed, refer to Appendix II below for more details on specific questions relating to renal dysfunction.

Appendix II
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 $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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.

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.

Checklist for Daily Data Collection

The checklist on the following page is a template designed to assist you with the data collection and to optimize enteral nutrition. This may be adapted to suit your needs.

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

Dietitian Daily Checklist

ICU Admission Date: _____ Patient Enrollment No # _____

Record these only once
(maximum kcals/protein prescribed)
Prescribed Energy Intake _____ Kcals
Prescribed Protein Intake _____grams

Use this format: dd/mon/year i.e. 01 May 2007
Date EN started in ICU_____
Date EN stopped in ICU_____
Date PN started in ICU_____
Date PN stopped in ICU_____

☐ EN never received
☐ PN never received

Study Day	1 (ICU admit)	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Calories Received (Kcals)															
Meeting >80% of Goal calories (Y/N)															
If No, comment															
Protein Received (grams)															
Meeting >80% of Goal protein (Y/N)															
If No, comment															
Type of Formula received (may select up to 3)															
EN interrupted due to feeding intolerance (Y/N)?															
If Yes to EN interrupted: Motility agents prescribed (Y/N)?															
If Yes to EN interrupted: Small bowel feeding tube placed? (Y/N)															
If Yes to EN interrupted: RD review requested? (Y/N)?															
EN interrupted due to fluid/ high urea concerns (Y/N)?															
If Yes, comment															
If on PN, type of lipids received															
PN interrupted due to fluid/ high urea concerns (Y/N)?															
If Yes, comment															

Study Day 1 is from ICU admission to the end of your 24 hr flowsheet.
Study Day 2 and subsequent days are the 24 hr period according to your flowsheet.

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

Dietitian Daily Checklist

ICU Admission Date: _____ Patient Enrollment No # _____

Study Day	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Calories Received (Kcals)															
Meeting >80% of Goal calories (Y/N)															
If No, comment															
Protein Received (grams)															
Meeting >80% of Goal protein (Y/N)															
If No, comment															
Type of Formula received (may select up to 3)															
EN interrupted due to feeding intolerance (Y/N)?															
If Yes to EN interrupted: Motility agents prescribed (Y/N)?															
If Yes to EN interrupted: Small bowel feeding tube placed? (Y/N)															
If Yes to EN interrupted: RD review requested? (Y/N)?															
EN interrupted due to fluid/ high urea concerns (Y/N)?															
If Yes, comment															
If on PN, type of lipids received															
PN interrupted due to fluid/ high urea concerns (Y/N)?															
If Yes, comment															