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

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

Administration of Study Supplements

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

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Study Groups

In the REDOXS© study, patients will receive both enteral and parenteral preparations from one of the following four treatment arms.

- Antioxidants (AOX)
- Glutamine (GLN)
- Glutamine and Antioxidants (GLN+AOX)
- Placebo

Components of the Study Groups for REDOXS© Study

Group	Enteral Supplement	Parenteral Supplement
AOX	AOX only	Placebo (normal saline) + Selenium
GLN	Glutamine only	Dipeptiven + Placebo (normal saline)
GLN +AOX	Glutamine + AOX	Dipeptiven + Selenium + Placebo (normal saline)
Placebo	Placebo	Placebo (normal saline)

The study supplements used in the REDOXS© study are to be considered as nutrients that are given at low doses (10-20 ml/hr). The unique design of the study allows these nutrients to be given independent of enteral or parenteral nutrition, thereby allowing for a better delivery.

- The enteral study supplements (EN REDOXS© formula) and the parenteral glutamine supplement (Dipeptiven) will be provided by Fresenius Kabi.

- The parenteral selenium (Micro-Selenium) will be supplied by BAXTER.

Dipeptiven

Micro-Selenium

Enteral REDOXS formulas

- Study supplements will be delivered to the site pharmacy before the start of the trial.

- The pharmacist/designate will be responsible for keeping a monthly inventory of the supplements and ordering more product.

Blinding

- All study personnel with the exception of the site pharmacist will be blinded to the allocation of the group the patient is randomized to. It is imperative that this blinding be maintained during the dispensing of the study supplements.

- To maintain blinding and to avoid a potential for bias, every attempt should be made to ensure that the Pharmacist dispensing the drugs is NOT the Pharmacist that participates in ICU rounds.

Start of Study Supplements

- Every effort should be made to ensure that both enteral and parenteral study supplements are started **within 2 hours of randomization and within 24 hours from admission to ICU.**

- Since the supplements are *nutrients* and are to be infused at low doses, it is safe to start them regardless of whether the patient is receiving enteral (or parenteral) feeds.

- Once the patient is resuscitated, the parenteral supplements can be started right away. The enteral supplements can be started once a nasogastric tube is in place and can be switched to a feeding tube subsequently.

Infusion of Study Supplements

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).

- The study supplements must be administered over 24 hours by continuous infusion provided by a dedicated intravenous pump and an enteral feeding pump.

- On Study Day 1 (from ICU admission to the end of your 24 hr flowsheet), depending upon when the patient is admitted, some patients may not receive their entire dose of the study supplements and this will have to be made up by doubling the infusion rate **up to a maximum of 12 hours** (i.e. to 20 cc/hr for the parenteral and 40 cc/hr for the enteral).

- Instructions for doubling the infusion rate for day 1:

    1) If more than 12 hours remaining until the end of study day 1: calculate the number of hours remaining until of study day 1 and divide the total prescribed volume over the remaining hours and infuse at this rate.

        Example for a 07:00-07:00 flowsheet and patient starts supplements at 12:00 hrs: there are 19 hours remaining, so divide the total volume over 19 hours = 480/19= 25 cc/hr (enteral) and 12.6 cc/hr (parenteral).

    2) If 12 hours or less remaining until end of study day 1: double the infusion rate until end of study day 1.
        Example for a 07:00-07:00 flowsheet and patient starts supplements at 22:00 hrs: double the rate from 22:00 hrs until 07:00 (for 9 hours). Volume of the study supplements received will be 360 enteral and 180 mls parenteral.

    3) Return to normal infusion rate at the start of the next study day = start of the next flowsheet

- Refer to **Appendix I Template of Orders.** The study coordinator is responsible to ensure that these orders are transcribed on to the Doctor's orders for each patient.

- Refer to "**Interruptions of Study Supplements"** on how to make up the volume.

Enteral Study Supplements

- Patients will receive the enteral study supplements for a minimum of 5 days and a maximum of 28 days (from randomization). These supplements will be discontinued once the feeding tube for enteral feeds is removed permanently.

- Enteral study supplements must have a separate administration bag and line. The enteral study supplements must NOT be mixed in the bag with the patient's enteral feed preparation.
    - If the patient is **not** on enteral feeds, the enteral study supplements will be delivered via a gastric or small bowel feeding tube.
    - If the patient **is already on** enteral feeds, a Y-connector must be added to the set up to allow delivery of the study supplements and the enteral feeding.

- Change enteral feeding tubing as per your hospital's protocol

- Once opened, the enteral study supplements can be stored at room temperature for 24 hours.

Parenteral Study Supplements

- Patients will receive the parenteral study supplements for a minimum of 5 days and a maximum of 28 days (from randomization).

- The parenteral study supplements MUST be infused through a **dedicated** port and should be infused through a central line (i.e. one port of a triple lumen port). A peripheral line can be used for infusion (72 hrs) until a central access can be obtained. See "Disruption of Central Line Access" for what to do if a central line access is lost.

- Change IV tubing as per your hospital's protocol.

- The compatibility and safety of the Dipeptiven with Selenium has been tested in a Dosing Study and there are no concerns.

> *The parenteral study supplements are to be mixed with saline but in the event of concerns of hypernatremia, the supplements can be mixed with D5W instead of saline. Compatibility studies of Dipeptiven and Selenium show that they are compatibility with saline and D5W.*

- **There is no information available on the compatibility of the parenteral study supplements with drugs and hence they are NOT to be infused with medication.**

- The parenteral study supplements are to be infused through a dedicated port but can be piggybacked with other IV replacement fluids such as dextrose, albumin, pentaspan and parenteral nutrition.

Prescribed Volumes

Every attempt should be made to ensure that the patients receive the entire dose of the study supplements prescribed in each 24-hour period. The prescribed volume will be calculated by the pharmacist and will appear on the products when they arrive in the ICU.

- For the enteral product, the prescribed infusion rate for ALL patients is 20 mL/hr X 24 hrs.
- For the parenteral preparation, the prescribed infusion rate will be 10 mL/hr X 24 hrs in most cases. In rare cases, if the patient is extremely tall, the parenteral study supplements may run at a higher rate. Refer to the label on the parenteral bag for the infusion rate (generated by the pharmacist).

Interruptions of Study Supplements

- Every attempt should be made to minimize interruptions to the infusion of the study supplements.

- The enteral study supplements should be held if the patient is to be NPO but should be restarted as soon as possible regardless of whether the patient is re-started on enteral feeds or not.

- The parenteral study supplements should be continued even if the patient is NPO. Every attempt should be made to make up for any deficit in the volume of the study supplements as a result of interruptions.

- If study supplements are disrupted or you are expecting them to be disrupted, please make up the deficit within that 24-hour period. Infusion rates may be doubled to achieve this. **You may double the infusion rates for a maximum of 12 consecutive hours, or up until the end of your flowsheet at which point the infusion rate resumes its previous hourly rate** (see Appendix I. Template for orders for day 1)**.** If you are unable to make up the deficit in that 24 hour period (according to your 24 hrs flowsheet), **DO NOT EXCEED THE TOTAL DAILY DOSE OF SUPPLEMENT PRESCRIBED** the following day.

If the volume of the study supplements received does not equal to that prescribed, this will be considered as a Protocol Violation or Protocol Deviation depending on the amount of volume received. Please refer to the Protocol Violation/Deviation section of the Study Binder for more details and how to report this.

Study Supplements and other Medications

- Do not infuse the parenteral study supplements with medications (a dedicated line is needed).

- The enteral (or the parenteral) study supplements DO NOT have to be held while administering medications such as dilantin, fluroquinolones, etc.

- The enteral study supplements can be mixed with medications as long as proper flushing techniques are followed.

Study Supplements in Renal Dysfunction

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. **Refer to Appendix II** for more details on specific questions relating to renal dysfunction.

Withholding the enteral and parenteral study supplements will be considered as a Protocol Violation or Protocol Deviation depending on the amount of volume received.
Please refer to the Protocol Violation/Deviation section of the Study Binder for more details and how to report this.

Study Supplements and SAEs

- In the event that a Serious Adverse Event (SAE) occurs that is possible or probably attributable to the study supplements, discontinue the study supplements.
- The Study coordinator is to proceed to fill out the appropriate SAE forms within 48 hours of becoming aware of the SAE (see SAE section of the binder).

Study Supplements at Discharge

- The study supplements are to be continued for a minimum of 5 days and a maximum of 28 days.
- Continue infusing the study supplements until the **"actual"** discharge from the ICU/hospital (i.e. the time that the patient actually leaves the ICU/hospital), rather than discontinuing them at the time the patient is "possibly" to be discharged.
- In the event a patient is ready to be discharged or discharged from ICU and the patient gets re-ventilated (**within 48 hours**) a nasogastric or feeding tube should be reinserted and both the parenteral and enteral study supplements should resume.

Continuation of Study Supplements beyond ICU
If the patient is discharged to the ward within 5 days from admission to ICU, the study supplements will be continued for a total of 5 days =120 hours, unless the patient is discharged from the ward to either another hospital or home.

- The **enteral study supplements** will be continued for this duration **ONLY** if there is a feeding tube in place for enteral feeds. If the feeding tube has been removed, the enteral study supplements will NOT be given.
- The **parenteral study supplements** will be continued for this duration even if the central line access has been disrupted. Refer to **Disruption of Central Line Access.**

If the patient is discharged to another facility or home within 5 days from admission to ICU, the study supplements will be discontinued at discharge.

Disruption of Central Line Access

- If central line access is disrupted, the parenteral supplements may be infused peripherally (for a period of up to 72 hours) to remain on schedule[1].
    - Peripheral infusions can be extended longer than 72 hours provided there are no signs of phlebitis/extravasations and this has been discussed with the Project Leader.

- If given peripherally, record signs of phlebitis/extravasations daily and enter on the web based data entry (Study Supplement Compliance page).
    - Refer to the Implementation manual (Study Supplement Compliance section) for definition of Phlebitis.

- In the event that you need to make up for deficits, the parenteral solution maybe infused at the double rate via the peripheral line but only for a maximum of 12 hours.

- Attempts to obtain a central line should continue to be made for optimal delivery of the parenteral supplements.

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

[1] Berg A et al. Clinical Nutrition 2002;21(2):135

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.

Enteral Feeding Intolerance

- It is vital to ensure that patients enrolled in the REDOXS© Study are receiving adequate calories and protein via enteral nutrition (or via parenteral nutrition if enteral route is contraindicated).
- Refer to the **Enteral Feeding Protocol (Appendix III)** for details on optimizing enteral feeding.
- The use of small bowel feeding tubes and motility agents is highly recommended.
- 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.

Stopping the Study Supplements

The **only** reason to stop the enteral study supplements prematurely would be an **absolute** contraindication of enteral nutrients i.e. in the event of:

Bowel Obstruction or
Bowel Perforation

Appendix I

Template for Orders for REDOXS© Study

- Height and admission weight to be documented on ICU flowsheet.
- Infuse Parenteral Study Supplements @ 10 ml/hr (as per pharmacy) via dedicated central line. May use peripheral line for up to 72 hours if central line access not available.
- Infuse Enteral Study Supplements @ 20 ml/hour via feeding tube.

(If more than 12 hours remaining in study day 1)

- Infuse Parenteral REDOXS supplements at _____cc/hr (calculate hourly rate by 240/#hrs) until __:__ hrs of next calendar day (date) (end of 24 hr flowsheet), then reduce rate to 10cc/hr.
- Infuse Enteral REDOXS supplements Day 1 (date) at _____cc/hr (calculate hourly rate by 480/#hrs) until __:__ hrs of next calendar day (date) (end of 24 hr flowsheet), then reduce rate to 20cc/hr.

(If ≤12 hours remaining in study day 1)

- On study day 1 (0700hr-0659hr) infuse both supplements at double the rate until __:__ hrs of next calendar day (date) (end of 24 hr flowsheet). Then resume normal rate as indicated above.

- Discontinue enteral feeds if feeding tube permanently removed, patient is NPO, patient develops bowel perforation or obstruction.
- Record hourly supplement infusions of both supplements on ICU flowsheet.
- Record interruptions of infusions on interruption sheet.
- Should an interruption occur, double infusion for number of interrupted hours (if able) up till __:__ (the end of your 24 hr flowsheet) for a maximum of 12 hours.
- Patient will receive a maximum of 28 days of study supplements while in ICU. If discharged to the ward within 5 days of ICU admission, the patient will receive a minimum of 5 days of study supplements =120 hours.
- Call Research RN at _____pager _____for any questions/concerns & when patient is discharged from ICU

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 ≥ 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).

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The REDOXS® Study
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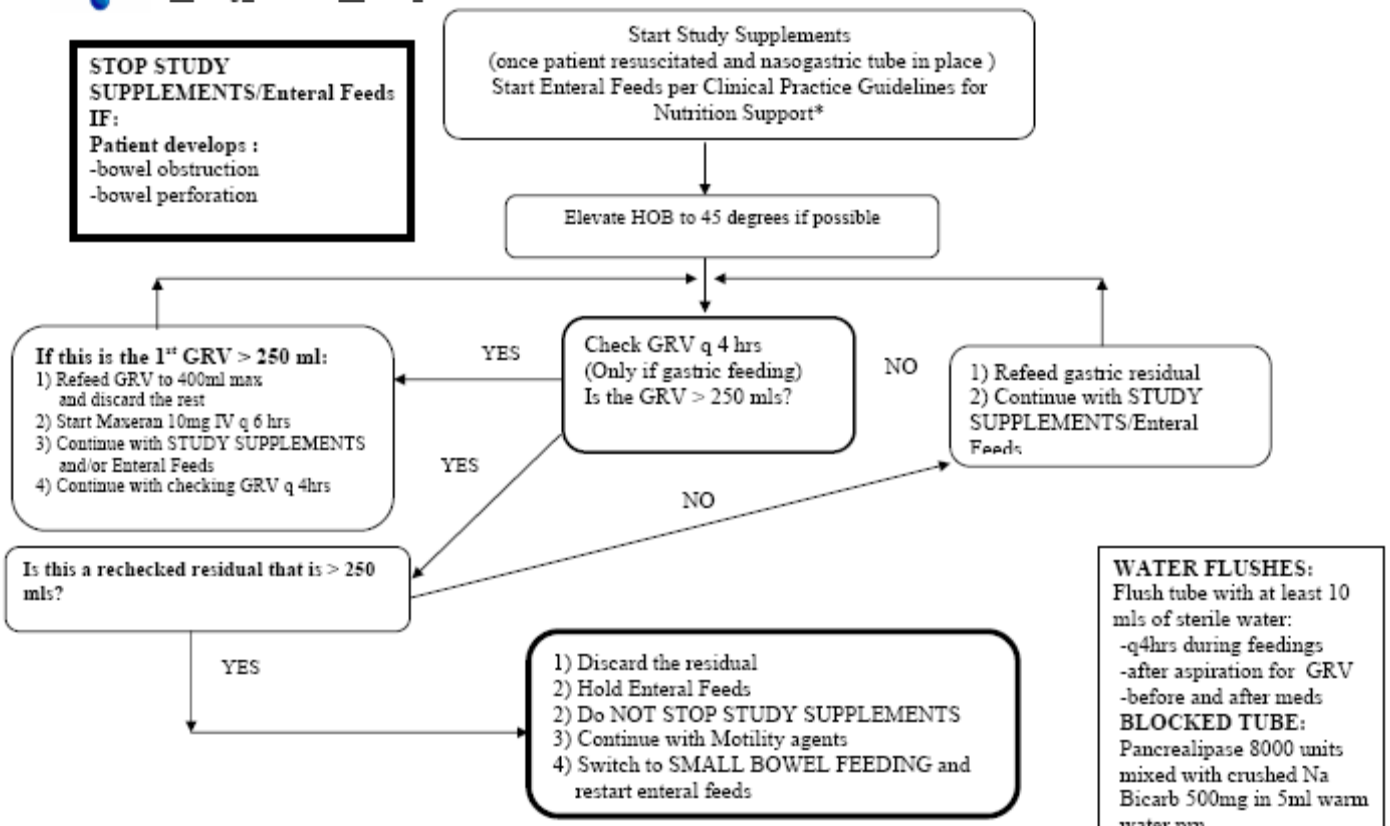
Appendix III Enteral Feeding Protocol



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