CRITICAL CARE NUTRITION SYSTEMATIC REVIEW: MASTER PROTOCOL

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BACKGROUND

Critical illness is defined as "A life-threatening process…that ultimately involves respiratory, cardiovascular and neurological compromise".[1] Critically ill patients are unable to consume adequate nutrition and need to be provided with artificial nutrition, also known as nutrition suppport.[2] Despite the widespread use of nutrition support, many areas in clinical practice remain controversial. There is a need to have a continuous update of the latest findings to assist practitioners to best optimize the benefits and minimize the risks of specialized nutrition support in critical illness.

Since 2003, our group has developed the "Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients" through systematic review and meta-analysis of randomized controlled trial (RCTs).[2] The aim of this guideline was to facilitate more effective, efficient, and consistent delivery of nutrition support that can lead to improved patient outcomes in the adult critical care setting. These guidelines were based on systematic reviews of the literature and meta-analyses were undertaken where appropriate. Over the years, these guidelines and associated systematic reviews were updated occasionally. In 2018, we ceased to create clinical practice guidelines but we have continued to update and publish systematic reviews on these related topics. Currently, there are 53 different topics and list of all the topics is available in **Appendix 1**.

We aim to continue this effort in developing and maintaining evidence-based systematic reviews for nutrition support in mechanically ventilated critically ill adults. The purpose of this document is to document the protocol of these ongoing systematic reviews in critical care nutrition with greater transparency.

METHODOLOGY

This systematic review will be conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guideline.[3]

Eligibility Criteria

The PICOS acronym is used to define the eligibility criteria for the systematic review (**Table 1**).

Table 1: PICOS Study Selection Criteria

Parameter	Inclusion Criteria
Population	Critically ill adult (critically ill is defined as being treated in ICU environment: i.e. either mechanically ventilated or if unable to determine this, mortality of >5% in the control group. Elective surgery patients are excluded)
Intervention	involve any form of enteral and/or parenteral nutrition or nutritional intervention
Comparator	The "standard care" in each topic. (For example: Early vs Delayed EN. Delayed EN is the control group) Or a predefined 'control group' (For example: The use of EN vs PN. PN is the control group)
Outcomes	Clinically important or patient-centered outcome (Must have one of the following: mortality, length of stay, infectious or other relevant complication, quality of life, muscle mass or functional status. Studies with only biochemical, metabolic or nutritional outcomes will be excluded.)
Study design	Randomized controlled trial (quasi trial will be excluded)

Information Sources and Search Strategy

The following databases will be searched from inception till the date of the planned update: MEDLINE, EMBASE and CENTRAL [Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials]) through OVID, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) through EBSCOhost. Language restriction will not be applied. The search strategies are predefined with the help of a librarian **(Appendix 2)**. In addition, we will search for additional articles from published systematic reviews, personal files and contacts.

Study Selection Process

A weekly alert is set up in OVID and EBSCOhost to deliver the latest result to our email. The result will then be imported to Covidence for systematic screening and review by 2 independent authors.

Data collection process

A standardized data abstraction form (DAF; **Appendix 3**) will be used to abstract relevant information independently by two authors.

For studies that reported median (Q1-Q3) for continuous outcomes, the corresponding authors will be contacted to obtain the mean and standard deviation (SD). If means and SDs were unavailable, the outcome will be excluded from the meta-analysis. For nutrition variables, the daily mean and SD of energy and protein delivery (the exact value) will be obtained from the primary publication or the corresponding author. If the precise estimate is unavailable because these data are only presented in a graph and authors are unable to provide the exact value, amounts of nutrition delivery will be estimated from the graph but not included in the meta-analysis.

Data Items

Outcomes

The following outcomes (per group) will be collected in the DAF:

a) Mortality (ICU, hospital, or any landmarked time point as defined by the primary publication)
b) Length of stays in the ICU and hospital
c) Duration on mechanical ventilation

d) Infectious or other relevant complications per patient such as ventilator-associated pneumonia, hospital-acquired infections, etc.
e) Muscle mass
f) Muscle strength
g) Physical function outcomes such as 6 minutes walk distance and other as defined by the primary publication
h) Quality of life outcomes
i) Gastrointestinal tolerance such as gastric residual volume, vomiting, regurgitation and diarrhea
j) Nutritional intake (energy in kcal/day or kcal/kg/day, protein in gram/day or gram/kg/day, fat and other micronutrients)
k) Nutritional indices such as nitrogen balance, blood glucose level, prealbumin and other as defined by the primary publication

Additional outcome may be collected depending on the topic under review.

Other variables

Other variables that will be collected in the DAF are:

a) Number of centers and nations involved in patient recruitment
b) Source of funding
c) Total number of patients randomized and analyzed
d) Patient population
e) Whether there were subgroup of malnourished patients analyzed
f) The composition of the study formula per group (if applicable)
g) Amount/dose of study intervention that are intended and received, per group (if applicable)

h) Timing of start of intervention, per group (intended and actual)

i) Duration of intervention, per group (intended and actual)

j) Whether the experimental and control diets intended to be isonitrogenous or isocaloric (if application)

k) Whether the experimental diet were given as pharmaconutrition.

Additional outcome may be collected depending on the topic under review.

Study Risk of Bias Assessment

Two independent authors will critically appraise an included study using the methodological quality scoring system that we have been using since the inception of this project. This scoring system ranges from 0 to 14 points (higher score indicates higher study quality; **Appendix 4**). Any disagreement will be resolved by a third author. A trial will be considered a level I study if all 3 of the following criteria were fulfilled: 1) concealed randomization, 2) double-blinded (outcome adjudication must be blinded) and 3) conducted an intention-to-treat analysis. If any one of the above characteristics was unfulfilled, it will be considered as a level II study. By using the same quality assessment tool since the beginning, we are able to compare methodological quality across time and across different sections.

Synthesis Methods and Data Analysis

A standardized table will be used to tabulate the outcomes of interest. An example of the table is presented in the **Appendix 5**. The table may be modified to suit the characteristics of certain topic.

Any missing or unclear information will be sought from the corresponding author. No assumption or data conversion will be made if we are unable to obtain these information, unless stated otherwise.

Meta-analysis will be conducted using RevMan 5.4 (Cochrane IMS, Oxford, UK). For dichotomized outcomes, the pooled risk ratio (RR) will be estimated by the DerSimonian and Laird random effect meta-analysis. For continuous outcomes, the random effect mean difference (MD) will be estimated. Heterogeneity will be quantified by the I^2 measure. The result of the meta-analysis will be presented in the forest plot generated by RevMan. A p-value $\leqslant 0.05$ was considered significant and values between >0.05 but <0.20 were considered a trend towards significance (for hypothesis-generating purpose).

Publication bias will be evaluated by funnel plot. Egger's test for funnel plot asymmetry will be performed by using the metafor package in RStudio (version 1.3.1093) if $\geqslant 10$ studies are included in a meta-analysis.[4]

Sensitivity or subgroup analysis will be conducted based on the requirement of each topic.

The following language will be used to describe the conclusion of the meta-analysis: 'is associated' if there was a significant difference between groups, 'may be associated' if there was a trend towards significant difference between groups, and 'has no effect' if there was insignificant difference between groups.

REFERENCES

1. Robertson LC, Al-Haddad M. Recognizing the critically ill patient. Anaesth Intensive Care Med. 2013;14(1):11-14. doi:10.1016/j.mpaic.2012.11.010.
2. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5):355-373. doi:10.1177/0148607103027005355
3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Published 2021 Mar 29. doi:10.1136/bmj.n71
4. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;342:1-8. doi:10.1136/bmj.d4002

APPENDIX 1: List of Topics

1.0 Indirect calorimetry vs. Predictive equations
2.0 The use of Enteral Nutrition vs Parenteral Nutrition
3.0 Enteral Nutrition (EN)
3.1 Early vs. Delayed EN
3.2 EN Energy Dose
3.2a Achieving Target Dose of EN
3.2b EN: Trophic vs Full Feeds
3.2c Hypocaloric EN
4.0 EN Composition
4.1 Pharmaconutrition
4.1a Composition of EN: Arginine and other nutrients
4.1b(i) Composition of EN: Fish oils, borage oils, & antioxidants
4.1b(ii)Composition of EN: Fish oils alone
4.1c Composition of EN: Glutamine
4.1d Composition of EN: Ornithine KetoGlutarate (OKG)
4.2 Composition of Macronutrients
4.2a Composition of EN: CHO/Fat: High fat/Low CHO
4.2b Composition of EN: CHO/Fat: Low fat/High CHO
4.2c Composition of EN: High Protein vs. Low Protein
4.3 Modification of Macronutrients
4.3a Composition of EN: Protein/peptides
4.3b Composition of EN: Fat Modified
4.4 Composition of EN: pH
4.5 Composition of EN: Fiber
4.6 Composition of EN: Prebiotics/Probiotics/Synbiotics
4.7 Composition of EN: HMB
5.0 EN Feeding Protocols
5.1 Feeding protocols (overall or components)
5.1a Feeding Protocols
5.1b Body Position
5.1c Fasting
5.2 Motility Agent & Intestinal Feeding
5.2a Use of Motility Agents
5.2b Motility Agents vs Intestinal Feeding
5.3 Gastric Residual Volumes (GRVs)
5.3a GRVs Thresholds
5.3b GRVs Monitoring
5.3c GRVs Frequency
5.3d Discarding GRVs
6.0 EN Administration
6.1 EN: Closed vs. Open Systems
6.2 EN: Small Bowel vs. Gastric Feeding
6.3 EN: Continuous vs. Other Methods of Administration
6.4 EN: Gastrostomy vs. Nasogastric Feeding
6.5 EN: Small Bowel vs. Gastric Feeding
7.0 Enteral and Parenteral Nutrition
7.1 Combination of Enteral and Parenteral Nutrition
7.2 Early vs. Delayed Supplemental Parenteral Nutrition

8.0 Parenteral Nutrition (PN)

8.1 PN vs. Standard Care

9.0 PN Composition

9.1a Composition of PN: Protein and Amino Acids

9.1b Composition of PN: Branched Chain Amino Acids

9.2a Composition of PN: Glutamine Supplementation

9.2b Composition of PN: Glutamine Supplementation + EN Supplementation

9.2c Composition of PN: EN + PN Glutamine

9.3 Composition of PN: Type of lipids

10.0 Strategies to optimize PN

10.1 Strategies to optimize PN: Hypocaloric vs Standard PN

10.2 Strategies to optimize PN: Use of lipids vs No lipids

10.3 Strategies to optimize PN: Mode of lipid delivery

11.0 Glycemic Control

11.1 Optimal glucose control: Insulin therapy

11.2 Optimal glucose control: Carbohydrate restricted formula + insulin therapy

12.0 Micronutrients

12.1 Antioxidant Nutrients: Combined Vitamins and Trace Elements

12.2 Antioxidant Nutrients: Parenteral Selenium (alone or in combination)

12.3 Antioxidant Nutrients: Parenteral Zinc (alone or in combination)

12.4 Vitamin C

12.5 Vitamin D

12.6 Thiamine

APPENDIX 2: Master Search Strategy

CONCEPT 1: Filter for RCT, Human and Adults

MEDLINE	EMBASE	CINAHL
1 randomized controlled trial.pt.	1. Randomized controlled trial/	S1 MH randomized controlled trials
2 controlled clinical trial.pt.	2. Controlled clinical study/	S2 MH double-blind studies
3 randomized.ab.	3. random$.ti,ab.	S3 MH single-blind studies
4 placebo.ab.	4. randomization/	S4 MH random assignment
5 drug therapy.fs.	5. intermethod comparison/	S5 MH pretest-posttest design
6 randomly.ab.	6. placebo.ti,ab.	S6 MH cluster sample
7 trial.ab.	7. (compare or compared or comparison).ti.	S7 TI (randomised OR randomized)
8 groups.ab.	8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	S8 AB (random*)
9 or/1-8	9. (open adj label).ti,ab.	S9 TI (trial)
	10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	S10 MH (sample size) AND AB (assigned OR allocated OR control)
	11. double blind procedure/	S11 MH (placebos)
	12. parallel group$1.ti,ab.	S12 PT (randomized controlled trial)
	13. (crossover or cross over).ti,ab.	S13 AB (control W5 group)
	14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	S14 MH (crossover design) OR MH (comparative studies)
	15. (assigned or allocated).ti,ab.	S15 AB (cluster W3 RCT)
	16. (controlled adj7 (study or design or trial)).ti,ab.	S16 MH animals+
	17. (volunteer or volunteers).ti,ab.	S17 MH (animal studies)
	18. human experiment/	S18 TI (animal model*)
	19. trial.ti.	S19 S16 OR S17 OR S18
	20. or/1-19	S20 MH (human)
	21. random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	S21 S19 NOT S20
	22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
	23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.	S23 S22 NOT S21
	24. (Systematic review not (trial or study)).ti.	
	25. (nonrandom$ not random$).ti,ab.	
	26. (Random field$).ti,ab.	
	27. (random cluster adj3 sampl$).ti,ab.	
	28. (review.ab. and review.pt.) not trial.ti.	
	29. (we searched).ab. and (review.ti. or review.pt.)	
	30. (update review).ab.	
	31. (databases adj4 searched).ab.	
	32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	

	33. Animal experiment/ not (human experiment/ or human/)	
	34. or/21-33	
	35. 20 not 34	
Children Filter		
10 (exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).in.) not exp adult/ (note: remove .kf for CENTRAL)	36 (exp adolescence/ or exp adolescent/ or exp child/ or exp childhood disease/ or exp infant disease/ or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or juvenile* or kid? or minors or minors* or neonat* or neo-nat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school or school child* or school* or schoolchild* or schoolchild*).ti,ab,kw. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).in. or (teen* or toddler? or underage? or under-age? or youth*).ti,ab,kw.) not exp adult/	S24 ((MH "Child+") or (MH "Adolescence")) NOT (MH "Adult+")
11 9 not 10	37 35 not 36	
Animals Filter		
12 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/	38 (animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.	-
13 ((animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.	39 (exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/	-
14 12 or 13	40 38 or 39	S25 S23 Not S24
15 11 not 14	41 37 not 40	

Note: CENTRAL already filtered for RCT and Human, therefore only the children filter was used

SOURCE of the Filters:

1. RCT filter: from Cochrane Handbook for Systematic Reviews of Interventions Version 6 Technical Supplement to Chapter 4: Searching for and selecting studies (https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl) (retrieved may 2021)
2. Children Filter: OVID expert search for children (https://tools.ovid.com/ovidtools/expertsearches.html) (retrieved may 2021)
3. Animal Filter: are from McGill University (https://www.muhclibraries.ca/training-and-guides/excluding-animal-studies/) (retrieved may 2021)

CONCEPT 2: Critically Ill Population (Combined with 'OR')

MeSH Terms (MEDLINE/CENTRAL)	Emtree (EMBASE)	MH Terms (CINAHL)	Keywords (all databases)
Critical care/ (Note: synonymous with intensive care) Critical illness/	Intensive care/ (Note: synonymous with critical care) critical illness/ critically ill patient/	(MH "Critical Care") (MH "Critical Illness") (MH "Critically Ill Patients")	critical care.mp. intensive care.mp. critical illness.mp. critically ill.mp.
Intensive care units/ burn units/ ~~respiratory care units/~~	intensive care unit/ ~~coronary care unit~~/ medical intensive care unit/ surgical intensive care unit/ neurological intensive care unit/ burn unit/	(MH "Intensive Care Units") ~~OR (MH "Coronary Care Units") OR (MH "Post Anesthesia Care Units") OR (MH "Respiratory Care Units") OR (MH "Stroke Units")~~	burn unit*.mp ~~respiratory care unit*.ti,kw.~~
Exp shock/ (includes: multiple organ failure, cardiogenic/ hemorrhagic/ surgical/ trauma shock, Systemic Inflammatory Response Syndrome, cytokine release syndrome, septic shock) sepsis/ ~~bacteremia/~~ ~~fungemia/~~	Exp shock/ (includes capillary leak syndrome, cardiogenic shock, dengue shock syndrome, experimental shock, hemorrhagic shock, hypovolemic shock, septic shock, toxic shock syndrome, traumatic shock) systemic inflammatory response syndrome/ sepsis/ ~~bacteremia/~~ ~~fungemia/~~ septic shock/ septicemia/ urosepsis/ multiple organ failure/	(MH "Shock+") (includes: Shock, Cardiogenic Shock, Hemorrhagic Shock, Septic Shock, Surgical Shock, Traumatic, systemic inflammatory response syndrome, cytokine release syndrome) (MH "Sepsis") ~~(MH "Bacteremia") OR (MH "Fungemia+")~~	Shock.ti,kw. Systemic inflammatory response syndrome.ti,kw. sepsis.mp. septic shock.mp. multiple organ dysfunction syndrome.ti,kw. multiple organ failure.ti,kw. cytokine release syndrome.ti,kw. ~~bacteremia.mp.~~ ~~fungemia.mp.~~
Respiratory Distress Syndrome/	respiratory distress syndrome/ acute lung injury/ adult respiratory distress syndrome/ transfusion related acute lung injury/	(MH "Respiratory Distress Syndrome") (MH "Respiratory Distress Syndrome, Acute") (MH "Acute Lung Injury+")	respiratory distress syndrome.ti,kw. acute lung injury.ti,kw. ~~COVID-19.mp.~~
Burns/	burn/ burn shock/	(MH "Burns") (MH "Burn Units") (MH "Burn Patients")	(burn* N3 patient*).ti,kw. Burn unit* (for CINHAL)
Multiple Trauma/	Multiple Trauma/	(MH "Multiple Trauma")	Multi* Trauma*.ti,kw. Multitrauma.ti,kw.
Pancreatitis, Acute Necrotizing/	acute pancreatitis/ ~~pancreatitis/~~ ~~acute hemorrhagic pancreatitis/~~	(MH "Pancreatitis, Acute Necrotizing")	Acute Necroti?ing Pancreatitis.ti,kw.
brain injuries/ brain injuries, traumatic/ ~~brain hemorrhage, traumatic/~~ ~~brain injuries, diffuse/~~ ~~Head Injuries, Closed/~~	brain injury/ ~~or acquired brain injury/ or brain concussion/ or brain contusion/ or brain damage/ or brain stem injury/ or cerebellum injury/ or diffuse brain injury/ or~~ traumatic brain injury/ ~~head injury/~~	(MH "Brain Injuries") ~~OR (MH "Brain Concussion") OR (MH "Brain Contusions") OR (MH "Left Hemisphere Injuries") OR (MH "Right Hemisphere Injuries")~~ ~~(MH "Head Injuries")~~	brain injur*.ti,kw. traumatic brain injur*.ti,kw. ~~traumatic brain hemorrhage.ti,kw.~~ ~~diffuse brain injur*.ti,kw.~~ ~~head injur*.ti,kw.~~

Respiration, artificial/ ~~Intubation, intratracheal/~~	exp artificial ventilation/ respiratory tract intubation/	(MH "Respiration, Artificial")	mechanical ventilat*.ti,kw. ~~intubat*.ti,kw.~~

.mp: multipurpose, .ti: title, .kw:keyword

Note: To make the search result more manageable, we used .ti,kw. for certain keywords and removed some of the less important terms (strikethrough)

CONCEPT 3: NUTRITION (Combined with 'OR')

MeSH Terms (MEDLINE/CENTRAL)	Emtree (EMBASE)	MH Terms (CINAHL)	Keywords (all databases)
Route, Dose, Timing			
nutritional support/ enteral nutrition/ parenteral nutrition/ parenteral nutrition, total/ (Note: Nutritional support is synonymous with Artificial feeding, Enteral Nutrition and Parenteral Nutrition (or intravenous feeding) is under the tree of Nutritional Support, artificial nutrition is not a MeSH) Intubation, Gastrointestinal/ (Note: synonymous with Nasogastric; Intubations)	nutritional support/ exp artificial feeding/ (note: artificial feeding includes digestive tract intubation, enteric feeding, nose feeding and parenteral nutrition)	(MH "Nutritional Support") (MH "Enteral Nutrition") (MH "Parenteral Nutrition") (MH "Peripheral Parenteral Nutrition") (MH "Total Parenteral Nutrition")	(nutrition* adj3 support*).mp. artificial nutrition.ti,kw. enteral nutrition.mp. ~~enteric feeding.ti,kw.~~ parenteral nutrition.mp. (parenteral adj3 infusion*).ti,kw. ~~intravenous feeding.ti,kw.~~ Gastrointestin* intubation.ti,kw.
~~Fasting/~~ ~~Standard care (IV fluids, oral diet etc, not EN)~~			~~fasting.ti,kw.~~
Enteral Formula			
Dietary supplements/ Food, Formulated/	Dietary supplement/ Elemental diet/ (use for food, formulated)	(MH "Dietary Supplements")	Enteral formula*.ti,kw. Nutrition* supplement*.ti,kw.
Macronutrients			
Carbohydrates/ Dietary carbohydrates/ Dietary fiber/	Carbohydrates/ Carbohydrate intake/ Carbohydrate diet/ Dietary fiber/	(MH "Carbohydrates") (MH "Dietary Carbohydrates") (MH "Dietary Fiber")	Carbohydrates.ti,kw. fiber.ti,kw. fibre.ti,kw.
Amino Acids/ Peptides/ Proteins/ exp dietary proteins/ protein hydrolysates/ Amino acids, branched-chain/ Leucine/	Amino Acids/ Peptides/ Proteins/ exp protein diet/ protein intake/ branched chain amino acid/ Leucine/	(MH "Amino Acids") (MH "Peptides") (MH "Proteins") (MH "Dietary Proteins") (MH "Leucine")	amino acid.ti,kw. peptide.ti,kw. protein.ti,kw. protein hydrolysates.ti,kw. branched chain amino acid*.ti,kw. leucine.ti,kw.
Lipids/ Fats/ Dietary Fats/ triglycerides/ Fat Emulsions, Intravenous/ fatty acids/ fatty acids, unsaturated/ fatty acids, essential/ exp fatty acids, omega-6/ exp Fatty Acids, Omega-3/ gamma-Linolenic Acid/ exp linoleic acids/ exp linolenic acids/ fish oils/ olive oil/ soybean oil/	Lipid/ Fat/ Fat intake/ Lipid diet/ Triacylglycerol/ Long chain triacylglycerol/ Medium chain triacylglycerol/ Exp Lipid emulsion/ (includes all brand of IV lipid emulsion such as intralipid, lipofundin etc) fatty acid/ essential fatty acid/ long chain fatty acid/ medium chain fatty acid/ unsaturated fatty acid/	(MH "Lipids") (MH "Fats") (MH "Dietary Fats") (MH "Triglycerides") (MH "Fat Emulsions, Intravenous") (MH "Fats, Unsaturated") (MH "Fatty Acids") (MH "Fatty Acids, Unsaturated") (MH "Fatty Acids, Essential") (MH "Linoleic Acids") (MH "Linolenic Acids+") (MH "Fatty Acids, Omega-3+")	Fats.ti,kw. Lipids.ti,kw. Triglycerides.ti,kw. Medium Chain Triglycerides.ti,kw. Long Chain Triglycerides.ti,kw. Polyunsaturated fatty acids.ti,kw. Fat emulsion.ti,kw. Lipid emulsion.ti,kw. Lipid injectable emulsion.ti,kw. Omega-3 fatty acid.ti,kw. Omega-6 fatty acid.ti,kw. Linoleic acid.ti,kw. Linolenic acid.ti,kw.

~~PN Lipid in total nutrient vs piggy back (no MeSH term)~~	omega 3 fatty acid/ linolenic acids/ (includes alpha linolenic acids) Docosahexaenoic acid/ Eicosapentaenoic Acid/ omega 6 fatty acid/ linoleic acids/ gamma-linolenic acid/ fish oils/ olive oil/ soybean oil/	[Includes alpha-Linolenic Acid, Docosahexaenoic Acids, Eicosapentaenoic Acid] (MH "Fatty Acids, Omega-6+") (Includes gamma-Linolenic Acid, Linoleic Acids) (MH "Fish oil") (MH "Soybean oil") (MH "Olive oil")	gamma-Linolenic Acid.ti,kw. Fish oil.ti,kw. Borage oil.ti,kw. Olive oil.ti,kw. Soybean oil.ti,kw. Parenteral adj3 lipid.ti,kw.
Energy Requirements			
Calorimetry, Indirect/ Basal Metabolism/	Indirect calorimetry/ Basal metabolic rate/ Energy expenditure/ Resting energy expenditure/	(MH "Calorimetry") (MH "Basal Metabolism+") (MH "Energy Metabolism")	Indirect calorimetry.ti,kw. basal metabolism.ti,kw. resting metabolic rate.ti,kw. basal metabolic rate.ti,kw. Resting energy expenditure.ti,kw. Predictive equation.ti,kw.
Micronutrients and Antioxidants			
Micronutrients/ Vitamins/ Trace Elements/ Antioxidants/ Ascorbic Acid/ Selenium/ ~~tocopherols/~~ ~~tocotrienols/~~ ~~vitamin e/~~ ~~alpha-tocopherol/~~ ~~beta-tocopherol/~~ ~~gamma-tocopherol/~~ ~~Copper/~~ ~~Manganese/~~ Zinc/ exp Vitamin D/ Thiamine/	Trace elements/ (use for micronutrients) Vitamin/ Antioxidant/ Selenium/ Zinc/ Ascorbic acid/ Vitamin D/ 25 hydroxyvitamin D/ Ergocalciferol/ Cholecalciferol/ Thiamine/	(MH "Micronutrients") (MH "Vitamins") (MH "Trace Elements") (MH "Antioxidants") (MH "Ascorbic Acid") (MH "Selenium") (MH "Zinc") (MH "Vitamin D+") (MH "Thiamine")	Micronutrients.ti,kw. Vitamins.ti,kw. Trace Elements.ti,kw. Antioxidants.ti,kw. Vitamin C.ti,kw. Ascorbic Acid.ti,kw. ~~Vitamin E.ti,kw.~~ ~~Tocopherols.ti,kw.~~ ~~Tocotrienols.ti,kw~~. Selenium.ti,kw. ~~Copper.ti,kw.~~ ~~Manganese.ti,kw.~~ Zinc.ti,kw. Vitamin D.ti,kw. Calcitriol.ti,kw. Cholecalciferol.ti,kw. Ergocalciferol.ti,kw. Vitamin B1.ti,kw. Thiamine.ti,kw.
Pharmaconutrition			
Glutamine/ Arginine/	Glutamine/ Arginine/	(MH "Glutamine") (MH "Arginine")	Glutamine.ti,kw. Arginine.ti,kw.
Other Special Additives			
No MeSH, just search keyword	No Emtree, just search for keyword	No MH, just search for keyword	ornithine ketoglutarate.ti,kw.
No MeSH, just search keyword	No Emtree, just search for keyword	No MH, just search for keyword	Beta-hydroxyl methylbutyrate.ti,kw.
Probiotics			
Probiotics/ Prebiotics/ Synbiotics/	Exp Probiotic agent/ (include Lactobacillus plantarum and saccharomyces boulardii)	(MH "Probiotics") (MH "Prebiotics") Note: no MH for Synbiotic	Probiotics.ti,kw. Prebiotics.ti,kw. Synbiotics.ti,kw.

	Prebiotic agent/ Synbiotic agent/		
EN tolerance and GRV			
~~Gastrointestinal Motility/~~ Gastric emptying/ ~~Gastrointestinal transit/~~ Gastroparesis/	Stomach emptying/ Stomach paresis/ Gastric suction/ (=gastric aspirate)	(MH "Gastrointestinal Motility") (MH "Gastroparesis")	~~Gastrointestinal Motility.ti,kw.~~ Gastric emptying.ti,kw. ~~Gastrointestinal transit.ti,kw.~~ Gastroparesis.ti,kw. Gastric residual volume.ti,kw.
Motility agents			
Gastrointestinal agent/ ~~Antiemetics/~~ ~~Cisapride/~~ ~~Domperidone/~~ ~~Erythromycin/~~ ~~Azithromycin/~~ ~~Metoclopramide/~~ ~~Alizapride (Not MeSH)~~ ~~Cinitapride (Cintapro/Pemix)~~ ~~Itopride (Ganaton)~~ ~~Lesuride (levosulpiride)~~ ~~Methylnaltrexon~~ ~~Mosapride~~	Gastrointestinal agent/ Prokinetic agent/	(MH "Gastrointestinal Agents")	Gastrointestinal agent.ti,kw. ~~Antiemetics.ti,kw.~~ ~~Cisapride.ti,kw.~~ ~~Domperidone.ti,kw.~~ ~~Erythromycin.ti,kw.~~ ~~Azithromycin.ti,kw.~~ ~~Metoclopramide.ti,kw.~~ Prokinetic agent.ti,kw. Motility agent.ti,kw.
Gastric vs Intestinal feeding			
Gastrostomy/ Jejunostomy/ Duodenostomy/	Gastrostomy/ Percutaneous endoscopic gastrostomy/ Jejunostomy/ Duodenostomy/	(MH "Gastrostomy") (MH "Jejunostomy") (note: No MH for Duodenostomy)	Gastrostomy.ti,kw. Jejunostomy.ti,kw. Duodenostomy.ti,kw. Gastric feeding.ti,kw. ~~Nasogastric feeding.ti,kw.~~ ~~Orogastric feeding.ti,kw.~~ Post pyloric feeding.ti,kw. Intestinal feeding.ti,kw. ~~Nasointestinal feeding.ti,kw.~~ ~~Nasojejunal feeding.ti,kw.~~ ~~Nasoduodenal feeding.ti,kw.~~ ~~Orojejunal feeding.ti,kw.~~ ~~Oroduodenal feeding.ti,kw.~~
EN feeding system			
No Mesh Term, search keyword	No Emtree, search keyword	No MH, search keyword	(enteral adj3 system).ti,kw. (feeding adj2 system).ti,kw.
EN continuous vs other mode of feeding			
No Mesh Term, search keyword	No Emtree, search keyword	No MH, search keyword	Continuous adj2 feeding.ti,kw. Bolus adj2 feeding.ti,kw. Intermittent adj2 feeding.ti,kw. Cyclic adj2 feeding.ti,kw.
Feeding protocol			
No Mesh Term, search keyword	No Emtree, search keyword	No MH, search keyword	Feeding protocol.ti,kw.
Body Position			
~~Patient positioning/~~ ~~Supine position/~~	~~No search~~	~~No search~~	~~Patient positioning.ti,kw.~~ ~~Supine position.ti,kw.~~

~~Prone position/~~			~~Prone position~~.ti,kw. ~~Body position~~.ti,kw. ~~(Semi?recumbent adj2 position)~~.ti,kw.
Blood Glucose Control			
Blood glucose/ Hyperglycemia/ Hypoglycemia/ Insulin/ ~~Hypoglycemic agents/~~	Glucose blood level/ Hyperglycemia/ Hypoglycemia/ Insulin/		Blood glucose.ti,kw. Hyperglycemi?.ti,kw. Hypoglycemi?.ti,kw. Insulin.ti,kw. ~~Hypoglycemic agent*~~.ti,kw.
pH			
~~Hydrogen Ion Concentration/~~	~~No search~~	~~No search~~	~~pH~~.ti,kw.

.mp: multipurpose, .ti: title, .kw:keyword

Note: To make the search result more manageable, we used .ti,kw. for certain keywords and removed some of the less important terms (strikethrough).

FINAL: Concept 1 AND 2 AND 3

APPENDIX 3: Data Abstraction Form

Critical Care Nutrition

Canadian Nutrition Support Clinical Practice Guidelines
Data Abstraction Form

First Author:
Journal Citation:
Country of origin of first Author:

Title of paper:

Purpose of the paper:

How many centers involved in recruiting patients:
How many nations:

Source of Funding: ☐ Industry ☐ Government or peer reviewed (non-industry)

☐ None specified ☐ Other, please specify:

Abstractor:
Date of Abstraction: (DD/MM/YYYY)

Inclusion Criteria	YES	NO
1. Is the study a randomized clinical trial or a meta-analysis?	☐	☐
a. What is the unit of analysis or randomization		
Patient	☐	
Clusters (ICU or hospital)	☐	
RCTs (meta-analysis)	☐	
2. Is target population critically ill adult humans? (critically ill is defined as being treated in ICU environment: i.e. either mechanically ventilated **or** if unable to determine this, mortality of >5% in the control group. Elective surgery patients are excluded).	☐	☐
3. Does the intervention involve any form of enteral and/or parenteral nutrition or nutritional intervention?	☐	☐
4. Are the study outcomes clinically important? (Must have one of the following: mortality, length of stay, infectious or other relevant complication, quality of life, muscle mass or functional status. Studies with only biochemical, metabolic or nutritional outcomes will be excluded.)	☐	☐
If YES to all of the above then study is included		

Canadian Nutrition Support Clinical Practice Guidelines
Data Abstraction Form

Author Name: **Abstractor Initials**:

1) Patient Population

A. Total number of patients randomized:
B. Total number of patients analyzed:
C. Please, describe patient population:
D. If critically ill specify illness case mix (i.e., proportion with trauma, burns, etc.):
E. If not all critically ill patients, please specify the quantity and nature of their illness:
F. Subgroup of Malnourished patients analyzed? ☐ Yes ☐ No

2) Study Intervention

EXPERIMENTAL GROUP:

A. composition:
B. amount/dose: intended & received:
C. timing of start of intervention: intended & actual:
D. duration of intervention: intended & actual:

CONTROL GROUP:

A. composition:
B. amount/dose: intended & received:
C. timing of start of intervention: intended & actual:
D. duration of intervention: intended & actual:

3) In your opinion, does the control group represent "usual care"?

☐ YES ☐ NO ☐ Don't Know ☐ Not applicable

a) Explain any issues:

4) Experimental and control diets intended to be isonitrogenous?

☐ YES ☐ NO ☐ Don't Know ☐ Not applicable

5) Experimental and control diets intended to be isocaloric?

☐ YES ☐ NO ☐ Don't Know ☐ Not applicable

6) Are the experimental nutrients provided dissociated from standard nutrition (pharmaconutrition concept)?

☐ YES ☐ NO ☐ Don't Know ☐ Not applicable

7) Comments:

APPENDIX 3: Data Abstraction Form (..continue)

CANADIAN NUTRITION SUPPORT CLINICAL PRACTICE GUIDELINES
Data Abstraction Form

Author Name: **Abstractor Initials**:

STUDY OUTCOMES: If more than one experimental group, please add an additional column. If N is different than overall N, include in N column.

Outcome		N	Experimental group, n=	Control group, n=	P value
Mortality	ICU				
	Hospital				
	Other, specify:				
	Not specified				
ICU length of stay[1] mean and SD median and ranges					
Hospital length of stay[1] mean and SD median and ranges					
Length of ventilation, day[2] mean and SD median and ranges					
Complications[2] # Infections/Infectious Complications per patients # Other complications **specify type(s):**					
Nutritional intake[3]					
Gastrointestinal tolerance[4]					
Muscle mass					
Muscle Strength					
Physical Function Outcomes					
Quality of Life					
Nutritional indices					
Other relevant outcomes **Specify:**					

[1]Length of stay and length of ventilation: Specify if reported as mean, median, standard error or standard deviation (mean and standard deviation are preferred).
[2]Report all complications that apply and the time over which the complications occurred. Record as follows: # patients with complications (preferred), # complications per group, # complications per patient
[3]Record as energy in kcal/day or kcal/kg/day, protein in gram/day or gram/kg/day, fat and other micronutrients
[4]Such as gastric residual volume, vomiting, regurgitation and diarrhea

APPENDIX 4: Methodological Quality Scoring System

Canadian Nutrition Support Clinical Practice Guidelines
Data Abstraction Form

Author Name: **Abstractor Initials**:

This scoring is for Randomized Controlled Trials only, not for meta-analyses

	Score		
	0	**1**	**2**
Randomization		Not concealed or not sure ☐	Concealed* randomization ☐
Analysis	Other ☐		Intention to treat ☐
Blinding	Not blinded ☐	Single blinded *Check who was blinded:* Health Care Professionals ☐ Outcomes Assessors ☐	Double blinded ☐
Patient selection	Selected patients or unable to tell ☐	Consecutive eligible patients ☐	
Comparability of groups at baseline	No or not sure ☐	Yes ☐	
Extent of follow-up	< 100% ☐	100% ☐	
Treatment protocol	Poorly described ☐	Reproducibly described ☐	
Co-interventions**	Not described ☐	Described but not equal or not sure ☐	Well described and all equal ☐
Outcomes	Not described ☐	Partially described ☐	Objectively defined ☐

Total Score: (max 14)

* Concealed randomization means the person enrolling the patients is unaware of the next treatment assignment (e.g. phone in randomization, computer generated).
** Extent to which antibiotics, ventilation, oxygen, transfusions, etc were applied equally across groups

APPENDIX 5: Example of Outcomes Summary Table

Table 1. Randomized studies evaluating early EN vs. delayed nutrient intake in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† Early EN	Mortality # (%)† Delayed	Infections # (%)‡ Early EN	Infections # (%)‡ Delayed
1) Moore 1986	Trauma with abdominal trauma index > 15 Shock (n=20) N=43	C.Random: not sure ITT: no Blinding: no (6)	Vivonex post op (< 24 hrs) via jejunostomy vs. D5W then progressed to parenteral nutrition if not on regular diet (both groups received PN)	1/32 (3)	2/31 (6)	3/32 (9)	9/31 (29)

Table 1. (…continued)

Study	LOS days Early EN	LOS days Delayed	Ventilator days Early EN	Ventilator days Delayed	Other Early EN	Other Delayed
1) Moore 1986	NR	NR	NR	NR	**Complications** 14/32 (44) **Feed Intolerance** 12/32 (38)	15/31 (48) NR

C.Random: Concealed randomization
ITT: Intent to treat
NR: Not reported
‡ Refers to the # of patients with infections unless specified
† Presumed hospital mortality unless otherwise specified
± ( ) : Mean ± SD =Standard deviation (number); (-) : mean (range) * SEM converted to SD

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