Recommendations, Quality of Evidence, and Recommendation Strength

Category or Condition	Recommendation	Quality of Evidence	Recommendation Strength
Nutrition Assessment	**Question: Does the use of a nutrition risk indicator identify patients who will most likely benefit from nutrition therapy?**		
	A1. Based on expert consensus, we suggest a determination of nutrition risk (for example NRS-2002, Nutric Score) be performed on all patients admitted to the ICU for whom volitional intake is anticipated to be insufficient. High nutrition risk identifies that patient most likely to benefit from early EN therapy.	Ungraded	
	Question: What additional tools, components or surrogate markers provide useful information when performing nutrition assessment in critically ill adult patients?		
	A2. Based on expert consensus, we suggest that nutritional assessment include an evaluation of co-morbid conditions, function of the gastrointestinal tract, and risk of aspiration. We suggest not using traditional nutrition indicators or surrogate markers, as they are not validated in critical care.	Ungraded	
	Question: What is the best method for determining energy needs in the critically ill adult patient?		
	A3a. We suggest that indirect calorimetry (IC) be used to determine energy requirements when available and in the absence of variables that affect the accuracy of measurement.	Very Low	Weak
Nutrition Assessment (cont)	A3b. Based on expert consensus, in the absence of IC, we suggest that a published predictive equation or a simplistic weight-based equation (25-30 kcal/kg/day) be used to determine energy requirements. (See section Q for obesity recommendations)	Ungraded	
	Question: Should protein provision be monitored independently from energy provision in critically ill adult patients?		

	A4. Based on expert consensus, we suggest an ongoing evaluation of adequacy of protein provision be performed.	Ungraded	
Initiate Enteral Nutrition	**Question: What is the benefit of early EN in critically ill adult patients when compared to withholding or delaying this therapy?**		
	B1. We recommend that nutrition support therapy in the form of EN should be initiated within the first 24-48 hours following onset of critical illness.	Very Low	Strong
	Question: Is there a difference in outcomes between the use of EN or PN for adult critically ill patients?		
	B2. We suggest the use of EN over PN in critically ill patients who require nutrition support therapy.	Very Low to Low	Weak.
Initiate Enteral Nutrition (cont)	**Question: Is the clinical evidence of contractility (bowel sounds, flatus) required prior to initiating EN in critically ill adult patients?**		
	B3. Based on expert consensus, we suggest that in the majority of medical and surgical ICU patient populations, while gastrointestinal contractility factors should be evaluated when initiating EN, overt signs of contractility should not be required prior to initiation of EN.	Ungraded	
	Question: What is the preferred level of infusion of EN within the GI tract for critically ill patients? How does the level of infusion of EN affect patient outcomes?		
	B4a. We recommend that the level of infusion be diverted lower in the GI tract in those critically ill patients at high risk for aspiration (see section D4) or those who have shown intolerance to gastric EN.	Moderate to High	Strong
	B4b. Based on expert consensus we suggest that in most critically ill patients it is acceptable to initiate EN in the stomach.	Ungraded	
	Question: Is EN safe during periods of hemodynamic instability in adult critically ill patients?		

	B5. Based on expert consensus, we suggest that in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and/or stable. Initiation/re-initiation of EN may be considered with caution in patients requiring low dose vasopressor support.	Ungraded	
Dosing of Enteral Nutrition	**Question: What population of patients in the ICU setting does not require nutrition support therapy over the first week of hospitalization?**		
	C1. Based on expert consensus, we suggest that patients who are at low nutrition risk with normal baseline nutrition status and low disease severity (for example NRS 2002 score< 3 or Nutric Score < 5) who cannot maintain volitional intake do not require specialized nutrition therapy over the first week of hospitalization in the ICU.	Ungraded	
	Question: For which population of patients in the ICU setting is it appropriate to provide trophic EN over the first week of hospitalization?		
	C2. We recommend that either trophic or full nutrition by EN is appropriate for patients with acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and those expected to have a duration of mechanical ventilation > 72 hours, as these two strategies of feeding have similar patient outcomes over the first week of hospitalization.	High	Strong
	Question: What population of patients in the ICU requires full EN (as close as possible to target nutrition goals) beginning in the first week of hospitalization? How soon should target nutrition goals be reached in these patients?		
	C3. Based on expert consensus, we suggest that patients who are determined to be at high nutrition risk (for example an NRS 2002 score >5 or Nutric score >6) or severely malnourished should be advanced towards goal as quickly as tolerated over 24-48 hours. Efforts to provide >80% of estimated or calculated goal energy and protein within 48-72 hours should be made in order to achieve the clinical benefit of EN over the first week of	Ungraded	

	hospitalization.		
	Question: Does the amount of protein provided make a difference in clinical outcomes of adult critically ill patients?		
	C4. We suggest that sufficient (high dose) protein should be provided. Protein requirements are expected to be in the range of 1.2 – 2.0 g/kg actual body weight per day, and may likely be even higher in burn or multi-trauma patients (See sections M and P).	Very Low	Weak
Monitoring Tolerance and Adequacy of Enteral Nutrition	**Question: How should tolerance of EN be monitored in the adult critically ill population?**		
	D1. Based on expert consensus, we suggest that patients should be monitored daily for tolerance of EN. We suggest that inappropriate cessation of EN should be avoided. We suggest that making the patient nil per os (NPO) surrounding the time of diagnostic tests or procedures should be minimized to limit propagation of ileus and to prevent inadequate nutrient delivery.	Ungraded	
	Question: Should GRVs be used as a marker for aspiration to monitor ICU patients on EN?		
	D2a. We suggest that GRVs not be used as part of routine care to monitor ICU patients on EN.	Low	Weak
	D2b. We suggest for those ICUs where GRVs are still utilized, that holding EN for GRVs <500 mL in the absence of other signs of intolerance (see D1) should be avoided.	Low	Weak
	Question: Should EN feeding protocols be used in the adult ICU setting?		
	D3a. We recommend that enteral feeding protocols should be designed and implemented to increase the overall percentage of goal calories provided.	Moderate to High	Strong
	D3b. Based on expert consensus we suggest that use of a volume-based feeding protocol or a top-down multi-strategy protocol be considered.	Ungraded	
	Question: How can risk of aspiration be assessed in critically ill adults patients receiving EN, and what measures may be taken to reduce the likelihood for aspiration pneumonia?		

	D4. Based on expert consensus, we suggest that patients placed on EN should be assessed for risk of aspiration, and that steps to reduce risk of aspiration and aspiration pneumonia should be proactively employed.	Ungraded	
	D4a. We recommend diverting the level of feeding by post-pyloric enteral access device placement in patients deemed to be at high risk for aspiration (see also B5)	Moderate to High	Strong
	D4b. Based on expert consensus, we suggest that for high-risk patients or those shown to be intolerant to bolus gastric EN, delivery of EN should be switched to continuous infusion.	Ungraded	
	D4c. We suggest that in patients at high risk of aspiration, agents to promote motility such as prokinetic medications (metoclopramide or erythromycin) be initiated where clinically feasible.	Low	Weak.
	D4d. Based on expert consensus, we suggest that nursing directives to reduce risk of aspiration and ventilator-associated pneumonia be employed. In all intubated ICU patients receiving EN, the head of the bed should be elevated 30-45º and use of chlorhexidine mouthwash twice a day should be considered.	Ungraded	
	Question: Are surrogate markers useful in determining aspiration in the critical care setting?		
	D5. Based on expert consensus, we suggest that blue food coloring or any coloring agent should not be used as a marker for aspiration of EN. Based on expert consensus, we also suggest glucose oxidase strips not be used as surrogate markers for aspiration in the critical care setting.	Ungraded	
	Question: How should diarrhea associated with EN be assessed in the adult critically ill population?		
	D6. Based on expert consensus, we suggest that EN not be automatically interrupted for diarrhea but rather feeds be continued while evaluating the etiology of diarrhea in an ICU patient to determine appropriate treatment.	Ungraded	
Set	**Question: Which formula should be used when initiating EN in the critically ill patient?**		

	E1. Based on expert consensus, we suggest using a standard polymeric formula when initiating EN in the ICU setting. We suggest avoiding the routine use of all specialty formulas in the critically ill patient in a medical ICU and disease-specific formulas in the surgical ICU.	Ungraded	
	Question: Do immune-modulating enteral formulations have an impact on clinical outcomes for the critically ill patient regardless of the ICU setting?		
	E2. We suggest immune-modulating enteral formulations [arginine with other agents including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), glutamine and nucleic acid] should not be used routinely in the medical ICU. Consideration for these formulations should be reserved for patients with traumatic brain injury and perioperative patients in the surgical ICU (see sections O, M).	Very Low	Weak
Selection of Appropriate Enteral Formulation (cont)	**Question: Should EN formulas with fish oils, borage oils and anti-oxidants be used in patients with acute lung injury or acute respiratory distress syndrome?**		
	E3. We cannot make a recommendation at this time regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (i.e., omega-3 fish oils, borage oil) and antioxidants, in patients with ARDS and severe acute lung injury (ALI) given conflicting data.	Low .	Weak
	Question: In adult critically ill patients, what are the indications, if any, for enteral formulations containing soluble fiber or small peptides?		
	E4a. We suggest that a commercial-mixed fiber formula not be used routinely in the adult critically ill patient prophylactically to promote bowel regularity or prevent diarrhea.	Low	Weak
	E4b. Based on expert consensus, we suggest considering use of a commercial-mixed fiber-containing formulations if there is evidence of persistent	Ungraded	

	diarrhea. We suggest avoiding both soluble and insoluble fiber in patients at high risk for bowel ischemia or severe dysmotility. We suggest considering use of small peptide formulations in the patient with persistent diarrhea with suspected malabsorption, risk for bowel ischemia or lack of response to fiber.		
Adjunctive Therapy	**Question: Should a fiber additive be used routinely in all hemodynamically stable ICU patients on standard enteral formulas? Should a soluble fiber supplement be provided as adjunctive therapy in the critically ill patient who develops diarrhea and is receiving a standard non-fiber containing enteral formula?**		
	F1. Based on expert consensus, we suggest that a fermentable soluble fiber (e.g. FOS, inulin) additive be considered for routine use in all hemodynamically stable medical and surgical ICU patients placed on a standard enteral formulation. We suggest that a fermentable soluble fiber supplement be given as adjunctive therapy if there is evidence of diarrhea.	Ungraded	
	Question: Is there a role for probiotic administration in critically ill patients? Is there any harm in delivering probiotics to critically ill patients?		
	F2. We suggest that while the use of studied probiotics species and strains appear to be safe in the general ICU patients, they should be used only for select medical and surgical patient populations where RCTs have documented safety and outcome benefit. We cannot make a recommendation at this time for the routine use of probiotics across the general population of ICU patients.	Very Low to Low	Weak
	Question: Does the provision of antioxidants and trace minerals affect outcome in critically ill adult patients?		
	F3. We suggest a combination of antioxidant vitamins and trace minerals in doses reported to be safe in critically ill patients be provided to those patients who require specialized nutrition therapy.	Low	Weak
	Question: Should enteral glutamine be provided to any subsets of patients in the adult ICU setting?		
	F4. We suggest that supplemental enteral glutamine **not be added** to an	Moderate	Weak

	enteral nutrition regimen routinely in critically ill patients.		
When to Use Parenteral Nutrition	**Question: When should parenteral nutrition be initiated in the adult critically ill patient at low nutritional risk?**		
	G1. We suggest in the patient who is at low nutrition risk (for example NRS 2002 score $\leq$ 3 or Nutric Score $\leq$ 5), exclusive parenteral nutrition (PN) should be withheld over the first 7 days following ICU admission in the patient who cannot maintain volitional intake and early EN is not feasible.	Very Low	Weak
	Question: When should PN begin in the critically ill patient at high nutrition risk?		
	G2. Based on expert consensus in the patient determined to be at high nutrition risk (for example an NRS 2002 score $\geq$5 or Nutric score $\geq$6) or severely malnourished, when EN is not feasible, we suggest initiating exclusive PN as soon as possible following ICU admission.	Ungraded	
	Question: What is the optimal timing for initiating supplemental PN when EN does not meet energy or protein goals in the patient at low or high nutrition risk?		
	G3. We recommend in patients at either low or high nutrition risk, use of supplemental PN be considered after 7 to 10 days if unable to meet > 60% of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this 7-10 day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient.	Moderate	Strong
When Indicated, Maximize Efficacy of Parenteral Nutrition	**Question: When PN is needed in the adult critically ill patient what strategies can be adopted to improve efficacy?**		
	H1. Based on expert consensus, we suggest the use of protocols and nutrition support teams to help incorporate strategies to maximize efficacy and reduce associated risk of PN.	Ungraded	
	Question: In the appropriate candidate (high risk or severely malnourished) for PN, should the dose be adjusted over the first week of hospitalization in the ICU?		
	H2. We suggest that hypocaloric PN dosing (≤ 20 kcal/kg/day or 80% of	Very Low	Weak

	estimated energy needs) with adequate protein (≥ 1.2 g protein/kg/day) be considered in appropriate (high risk or severely malnourished) patients requiring PN, initially over the first week of hospitalization in the ICU.		
	Question: Should soy-based IV fat emulsions (IVFE) be provided in the first week of ICU stay? Is there an advantage of using alternative IVFE (i.e., MCT, olive oil, fish oil, mixture of oils) over traditional soybean oil-based lipid emulsions in critically ill adult patients?		
	H3a. We suggest withholding soy-based IVFE during the first week following initiation of PN in the critically ill patient unless the patient has high-risk of essential fatty acid deficiency.	Very Low	Weak
When Indicated, Maximize Efficacy of Parenteral Nutrition	H3b Alternative IVFE may provide outcome benefit over soy-based IVFE, however we cannot make a recommendation at this time due to lack of availability of these products in the U.S. When these alternative IVFE (SMOF, MCT, OO and FO) become available in the U.S. based on expert opinion, we suggest their use be considered in the critically ill patient who is an appropriate candidate for PN.	Ungraded	
	Question: Is there an advantage to using standardized commercially-available PN (pre-mixed PN) versus compounded PN admixtures?		
	H4. Based on expert consensus, use of standardized commercially-available PN vs. compounded PN admixtures in the ICU patient has no advantage in terms of clinical outcomes.	Ungraded	
	Question: What is the desired target blood glucose range in adult ICU patients?		
	H5. We recommend a target blood glucose range of 140-150 to180 mg/dL for the general ICU population; ranges for specific patient populations (post cardiovascular surgery, head trauma) may differ and is beyond the scope of this guideline.	Moderate	Strong
	Question: Should parenteral glutamine be used in the adult ICU patient?		

	H6. We recommend that parenteral glutamine supplementation not be used routinely in the critical care setting.	Moderate	Strong
	Question: In transition feeding, as an increasing volume of EN is tolerated by a patient already receiving PN, at what point should the PN be terminated?		
	H7. Based on expert consensus, we suggest as tolerance to EN improves, the amount of PN energy should be reduced and finally discontinued when the patient is receiving > 60% of target energy requirements from EN.	Ungraded	
Pulmonary Failure	**Question: What is the optimal carbohydrate to fat ratio for the adult ICU patient with pulmonary failure?**		
	I1. We suggest that specialty high fat: low carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO2 production not be used in ICU patients with acute respiratory failure (not to be confused with recommendation E3).	Very Low	Weak
	Question: Does use of energy-dense EN formulas to restrict fluid administration benefit the adult ICU patient with acute respiratory failure?		
	I2. Based on expert consensus, we suggest that fluid-restricted energy dense EN formulations should be considered for patients with acute respiratory failure (especially if in state of volume overload).	Ungraded	
	Question: Should serum phosphate concentrations be monitored when EN or PN is initiated in the ICU patient with respiratory failure?		
	I3. Based on expert consensus, we suggest that serum phosphate concentrations should be monitored closely, and phosphate replaced appropriately when needed.	Ungraded	
Renal Failure / Acute Kidney Injury	**Question: In adult critically ill patients with acute kidney injury (AKI), what are the indications for use of specialty enteral formulations? What are appropriate energy and protein recommendations to reduce morbidity in AKI?**		
	J1. Based on expert consensus, we suggest that ICU patients with acute renal failure (ARF) or AKI should be placed on a standard enteral formulation, and	Ungraded	

	standard ICU recommendations for protein (1.2 – 2 g/kg actual body weight per day) and energy (25-30 kcal/kg/day) provision should be followed. If significant electrolyte abnormalities develop, a specialty formulation designed for renal failure (with appropriate electrolyte profile) may be considered.		
	Question: In adult critically ill patients with AKI receiving hemodialysis or continuous renal replacement therapy, what are appropriate targets for protein intake to support increased nitrogen losses?		
	J2. We recommend that patients receiving hemodialysis or continuous renal replacement therapy (CRRT) should receive increased protein, up to a maximum of 2.5 g/kg/day. Protein should not be restricted in patients with renal insufficiency as a means to avoid or delay initiating dialysis therapy.	Very Low	Weak
Hepatic Failure	**Question: Should energy and protein requirements be determined similarly in critically ill patients with hepatic failure as those without hepatic failure?**		
	K1. Based on expert consensus, we suggest a dry weight or usual weight be used instead of actual weight in predictive equations to determine energy and protein in patients with cirrhosis and hepatic failure, due to complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia. We suggest nutrition regimens avoid restricting protein in patients with liver failure, using the same recommendations as other critically ill patients (see section C4).	Ungraded	
Hepatic Failure	**Question: What is the appropriate route of nutrition delivery in patients with hepatic failure?**		
	K2. Based on expert consensus, we suggest EN be used preferentially when providing nutrition therapy in ICU patients with acute and/or chronic liver disease.	Ungraded	
	Question: Is a disease-specific enteral formulation needed for critically ill patients with liver disease?		
	K3. Based on expert consensus, we suggest standard enteral formulations should be used in ICU patients with acute and chronic liver disease. There is	Ungraded	

	no evidence of further benefit of branched chain amino acid formulations (BCAA) on coma grade in the ICU patient with encephalopathy who is already receiving first-line therapy with luminal acting antibiotics and lactulose.		
	Question: Does disease severity in acute pancreatitis influence decisions to provide specialized nutrition therapy?		
	L1a. Based on expert consensus, we suggest the initial nutrition assessment in acute pancreatitis evaluate disease severity to direct nutrition therapy. Since disease severity may change quickly, we suggest frequent reassessment of feeding tolerance and need for specialized nutrition therapy.	Ungraded	
Acute Pancreatitis	**Question: Do patients with mild acute pancreatitis need specialized nutrition therapy?**		
	L1b. We suggest not providing specialized nutrition therapy to patients with mild acute pancreatitis, instead advancing to an oral diet as tolerated. If an unexpected complication develops or there is failure to advance to oral diet within 7 days, then specialized nutrition therapy should be considered. L1c. We suggest that patients with moderate to severe acute pancreatitis should have a naso/oroenteric tube placed and EN started at a trophic rate and advanced to goal as fluid volume resuscitation is completed (within 24-48 hours of admission) (Very Low/Weak)	Very Low	Weak
	Question: Which is the most appropriate formula to use when initiating early EN in the patient with moderate to severe acute pancreatitis?		
	L2. We suggest using a standard polymeric formula to initiate EN in the patient with severe acute pancreatitis. Although promising, the data are currently insufficient to recommend placing a patient with severe acute pancreatitis on an immune-enhancing formulation at this time.	Very Low	Weak
	Question: Should patients with severe acute pancreatitis receive EN or PN?		
	L3a. We suggest the use of EN over PN in patients with severe acute	Very Low	Weak

	pancreatitis that require nutrition therapy.		
	Question: Should patients with severe acute pancreatitis be fed into the stomach or small bowel?		
	L3b. We suggest that EN be provided to the patient with severe acute pancreatitis by either the gastric or jejunal route, as there is no difference in tolerance or clinical outcomes between these two levels of infusion.	Very Low	Weak
	Question: In the presence of intolerance, what strategies can be used to enhance tolerance to EN in patients with severe acute pancreatitis?		
	L4. Based on expert consensus, we suggest in patients with moderate to severe acute pancreatitis who have intolerance to EN, measures should be taken to improve tolerance.	Ungraded	
	Question: Should patients with severe acute pancreatitis receive probiotics?		
	L5. We suggest that use of probiotics be considered in patients with severe acute pancreatitis who are receiving early EN.	Low	Weak
	Question: When is it appropriate to use PN in patients with severe acute pancreatitis?		
	L6. Based on expert consensus, we suggest that for the patient with severe acute pancreatitis, when EN is not feasible, use of PN should be considered after one week from the onset of the pancreatitis episode.	Ungraded	
Surgical Subsets Trauma	**Question: Does the approach for nutrition therapy for the trauma patient differ from that of other critically ill patients?**		
	M1a. We suggest that similar to other critically ill patients, early enteral feeding with a high protein polymeric diet be initiated in the immediate post-trauma period (within 24 to 48 hours of injury) once the patient is hemodynamically stable.	Very Low	Weak
Trauma	**Question: Should immune-modulation formulas be used routinely to improve outcomes in a patient with severe trauma?**		
	M1b. We suggest that immune-modulating formulations containing arginine and fish oil be considered in patients with severe trauma.	Very Low	Weak

Surgical Subsets Traumatic Brain Injury	**Question: Does the approach for nutrition therapy for the traumatic brain injury (TBI) patient differ from that of other critically ill patients or trauma patients without head injury?**		
	M2a. We recommend that similar to other critically ill patients, early enteral be initiated in the immediate post-trauma period (within 24 to 48 hours of injury) once the patient is hemodynamically stable.	Very Low .	Weak
	Question: Should immune-modulating formulas be used in a patient with TBI?		
	M2b: Based on expert consensus, we suggest the use of either arginine-containing immune-modulating formulations or EPA/DHA supplement with standard enteral formula in patients with TBI.	Ungraded	
Surgical Subsets Open Abdomen	**Question: Is it safe to provide EN to patients with an open abdomen?**		
	M3a. Based on expert consensus, we suggest early EN (24 - 48 hours post injury) in patients treated with an open abdomen (OA) in the absence of bowel injury.	Ungraded	
	Question: Do patients with open abdomen have increased protein or energy needs?		
	M3b. Based on expert consensus, we suggest providing an additional 15 to 30 grams protein per liter of exudate lost for patients with open abdomen (with energy provision similar to other patients in a surgical ICU setting). Energy needs should be determined as for other ICU patients (see section A).	Ungraded	
Surgical Subsets Burns	**Question: What mode of nutrition support should be used to feed burn patients?**		
	M4a. Based on expert consensus EN should be provided to the burn patient whose gastrointestinal tract is functional and volitional intake is inadequate to meet estimated energy needs. PN should be reserved for those burn patients for whom EN is not feasible or not tolerated.	Ungraded	
	Question: How should energy requirements be determined in burn patients?		
	M4b. Based on expert consensus, we suggest that IC be used when available to assess energy needs in burn patients with weekly repeated measures.	Ungraded	

	Question: What is the optimal quantity of protein to deliver to patients with large burns requiring ICU care?		
	M4c. Based on expert consensus, we suggest that patients with burn injury should receive protein in the range of 1.5 to 2g/kg/day.	Ungraded	
	Question: When should nutrition support be initiated in a patient with burn injury?		
	M4d. Based on expert consensus, we suggest very early initiation of EN (if possible within 4-6 hours of injury) in a patient with a burn injury.	Ungraded	
Sepsis	**Question: Are patients with severe sepsis candidates for early enteral nutrition therapy?**		
	N1. Based on expert consensus, we suggest that critically ill patients receive EN therapy within 24-48 hours of making the diagnosis of severe sepsis/septic shock as soon as resuscitation is complete and the patient is hemodynamically stable.	Ungraded	
	Question: Should exclusive or supplemental PN be added to EN providing < 60% of goal in the septic patient?		
	N2. We suggest not using PN alone or in conjunction with EN early in the first week after the diagnosis of severe sepsis or septic shock is made, regardless of their degree of nutrition risk.	Very Low	Weak
	Question: What is the optimal micronutrient supplementation in sepsis?		
	N3. We cannot make a recommendation regarding selenium, zinc and antioxidant supplementation in sepsis at this time due to conflicting studies.	Moderate	Weak
	Question: What are the protein and energy requirements for septic patients in the acute phase of management?		
	N4. Based on expert consensus, we suggest the provision of trophic feeding (defined as up to 500 kcal/day) for the initial phase of sepsis, advancing as tolerated after 24-48 hours to > 80% of target energy goal over the first week. We suggest delivery of 1.2 to 2 g protein/kg/day.	Ungraded	
	Question: Is there any advantage to providing immune or metabolic-modulating enteral formulations (arginine with other agents including EPA, DHA, glutamine and nucleic acid) in sepsis?		
	N5. Based on expert consensus, we suggest immune-modulating formulas	Ungraded	

	should not be used routinely in patients with severe sepsis.		
Post-operative Major Surgery (SICU Expected)	**Question: Is the use of a nutrition risk indicator to identify patients who will most likely benefit from post-operative nutrition therapy more useful than traditional markers of nutrition assessment?**		
	O1. Based on expert consensus, we suggest determination of nutrition risk (for example NRS-2002 or Nutric Score) be performed on all post-operative patients in the ICU and that traditional "visceral protein levels" (serum albumin, prealbumin and transferrin concentrations) should not be used as markers of nutrition status.	Ungraded	
	Question: What is the benefit of providing EN early in the post-operative setting compared to providing PN or STD		
	O2. We suggest that EN be provided when feasible in the post-operative period within 24 hours of surgery, as it results in better outcomes than use of PN or STD.	Very Low	Weak
	Question: Should immune-modulation formulas be used routinely to improve outcomes in a post-operative patient?		
	O3. We suggest the routine use of an immune-modulating formula (containing both arginine and fish oils) in the surgical ICU for the post-operative patient who requires EN therapy.	Low to Moderate	Weak
	Question: Is it appropriate to provide EN to a surgical ICU patient in the presence of difficult post-operative situations such as open abdomen, bowel wall edema, fresh intestinal anastomosis, vasopressor therapy, or ileus?		
	O4. We suggest enteral feeding for many patients in difficult post-operative situations such as prolonged ileus, intestinal anastomosis, open abdomen, and need of vasopressors for hemodynamic support. Each case should be individualized based on perceived safety and clinical judgment.	Low	Weak
	Question: When should PN be used in the post-operative ICU patient?		
	O5. Based on expert consensus, we suggest that for the patient who has undergone major upper GI surgery and EN is not feasible; PN should be initiated (only if the duration of therapy is anticipated to be >7 days). PN	Ungraded	

	should not be started in the immediate post-operative period, but should be delayed for 5-7 days.		
	Question: Is advancing to a clear liquid diet required as the first volitional intake in the post-operative ICU patient?		
	O6. Based on expert consensus, we suggest that upon advancing the diet post-operatively, patients be allowed solid food as tolerated and that clear liquids are not required as the first meal.	Ungraded	
Chronically Critically Ill	**Question: How should the chronically critically ill patient be managed by nutrition therapy?**		
	P1. Based on expert consensus, we suggest that the chronically critically ill patient (defined as those requiring mechanical ventilation greater than 21 days) be managed with aggressive high protein enteral nutrition therapy, and when feasible, that a resistance exercise program be used.	Ungraded	
Obesity in Critical Illness	**Question: Do obese ICU patients benefit less from early EN in the first week of hospitalization, due to their nutrition reserves, than their lean counterparts?**		
	Q1. Based on expert consensus, we suggest early EN to start within 24-48 hours of admission to the ICU for the obese patient who cannot sustain volitional intake.	Ungraded	
	Question: What additional parameters should be addressed with a nutrition assessment in critical illness when the patient is obese?		
	Q2. Based on expert consensus we suggest that nutrition assessment of the obese ICU patient focus on biomarkers of the metabolic syndrome, an evaluation of comorbidities, and a determination of level of inflammation in addition to those described for all ICU patients	Ungraded	
	Question: What factors on assessment identify obese patients in the ICU to be at high risk?		
	Q3. Based on expert consensus, we suggest that nutrition assessment of the obese ICU patient focus on evidence of central adiposity, metabolic syndrome,	Ungraded	

	sarcopenia, BMI >40, SIRS, or other comorbidities that correlate with higher obesity-related risk for cardiovascular disease and mortality.		
	Question: In adult ICU obese patients, does use of high protein, hypocaloric feeding improve clinical outcomes compared with use of high protein, eucaloric feeding?		
	Q4. Based on expert consensus, we suggest that high protein hypocaloric feeding be implemented in the care of the obese ICU patient to preserve lean body mass, mobilize adipose stores, and minimize the metabolic complications of overfeeding.	Ungraded	
Obesity in Critical Illness (cont)	**Question: In adult ICU obese patients, what are the appropriate targets for energy and protein intake to achieve nitrogen equilibrium and meet metabolic requirements?**		
	Q5. Based on expert consensus, we suggest for all classes of obesity that the goal of the EN regimen should not exceed 65-70% of target energy requirements as measured by IC. If IC is unavailable, we suggest using the weight-based equation 11-14 kcal/kg actual body weight/day for patients with BMI in the range 30-50 and 22-25 kcal/kg ideal body weight/day for patients with BMI >50. We suggest that protein should be provided in a range from 2.0 g/kg ideal body weight/day for patients with BMI 30-40 up to 2.5 g/kg ideal body weight/day for patients with BMI ≥ 40.	Ungraded	
	Question: What indications exist, if any, for use of specialty enteral formulations for adult ICU obese patients?		
	Q6. Based on expert consensus, we suggest that if available an enteral formula with low caloric density and a reduced nonprotein calorie:nitrogen be used in the obese adult ICU patient. While an exaggerated immune response in obese patients implicates potential benefit from immune-modulating formulas, lack of outcomes data precludes a recommendation at this time.	Ungraded	
al Illnes	**Question: What are appropriate monitors to follow for the obese critically ill patient receiving early EN?**		
	Q7. Based on expert consensus, we suggest additional monitoring to assess	Ungraded	

	worsening of hyperglycemia, hyperlipidemia, hypercapnia, fluid overload, and hepatic fat accumulation in the obese critically ill patient receiving EN.		
	Question: Does the obese ICU patient with a history of bariatric surgery or other malabsorptive condition require any additional supplementation of micronutrients when starting nutrition therapy?		
	Q8. Based on expert consensus, we suggest that the obese ICU patient with a history of bariatric surgery receive supplemental thiamine prior to initiating dextrose-containing IV fluids or nutrition therapy. In addition, evaluation for and treatment of micronutrient deficiencies such as calcium, thiamin, vitamin B12, fat-soluble vitamins (A,D,E,K), and folate, along with the trace minerals iron, selenium, zinc, and copper should be considered.	Ungraded	
Nutrition Therapy End-of-Life Situations	**Question: What is the role of artificial nutrition and hydration (ANH) in end-of-life situations?**		
	R1. Based on expert consensus, we suggest ANH is not obligatory in cases of futile care or end-of-life situations. The decision to provide ANH should be based on evidence, best practices, clinical experience and judgment, effective communication with the patient, family and/or authorized surrogate decision maker, and respect for patient autonomy and dignity.	Ungraded	

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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/vvvv

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, quality of life, functional status or complications. 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: _____

A. Patient population

1) Total number of patients randomized: _____
2) Please, describe patient population
3) If critically ill specify illness case mix
   (i.e., proportion with trauma, burns, etc.)

4) If not all critically ill patients, please specify the quantity and nature of their illness

5) Subgroup of Malnourished patients analyzed?

☐ Yes ☐ No

B. Study intervention

Specify for both experimental and control:

1) composition

Experimental

2) amount/dose: intended & received
3) timing of start of intervention: intended & received
4) duration of intervention: intended and actual

Control

In your opinion, does the control group represent "usual care" ☐ YES ☐NO ☐ Don't Know ☐Not applicable
Explain any issues: _____

_____

Experimental and control diets intended to be isonitrogenous ☐ YES ☐NO ☐ Don't Know ☐Not applicable

Experimental and control diets intended to be isocaloric ☐ YES ☐NO ☐ Don't Know ☐Not applicable

Are the experimental nutrients provided dissociated from standard nutrition (pharmaconutrition concept): ☐ YES ☐NO ☐ Don't Know ☐Not applicable

Comments:_____

Canadian Nutrition Support Clinical Practice Guidelines
Data Abstraction Form

Author name:_____ Abstractor initials: _____

C. Study Outcomes[1] : **if more than one experimental/control group, list all**

		Experimental group (n=_____)	**Control group**	P value
Mortality	ICU			
	Hospital			
	Other (specify what type)			
	Not specified			

[1] Report results of intention to treat analysis on all patients randomized, if possible.

ICU length of stay[2] mean and SD median and ranges			
Hospital length of stay[2] mean and SD median and ranges			
Complications[3] # Infections/Infectious complications **(specify type)** # Other complications **(specify types)**			
Length of ventilation[2] mean and SD			
Nutritional intake			
Nutritional indices			
Other relevant outcomes			

[2] Length of stay and length of ventilation: Specify if reported as mean, median, Standard Error or Standard Deviation (latter is preferred).

[3] 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

Canadian Nutrition Support Clinical Practice Guidelines
Methodology Scoring

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 blind ☐	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, TPN, ventilation, oxygen, transfusions, etc were applied equally across groups

Abstractor's conclusions:

_____
_____
_____

Additional GRADE and Forest Plots

Should. EN vs. IV fluids/NPO be used in critically ill patient?

Question: Early EN vs. delayed nutrient intake for Studies from WEBER

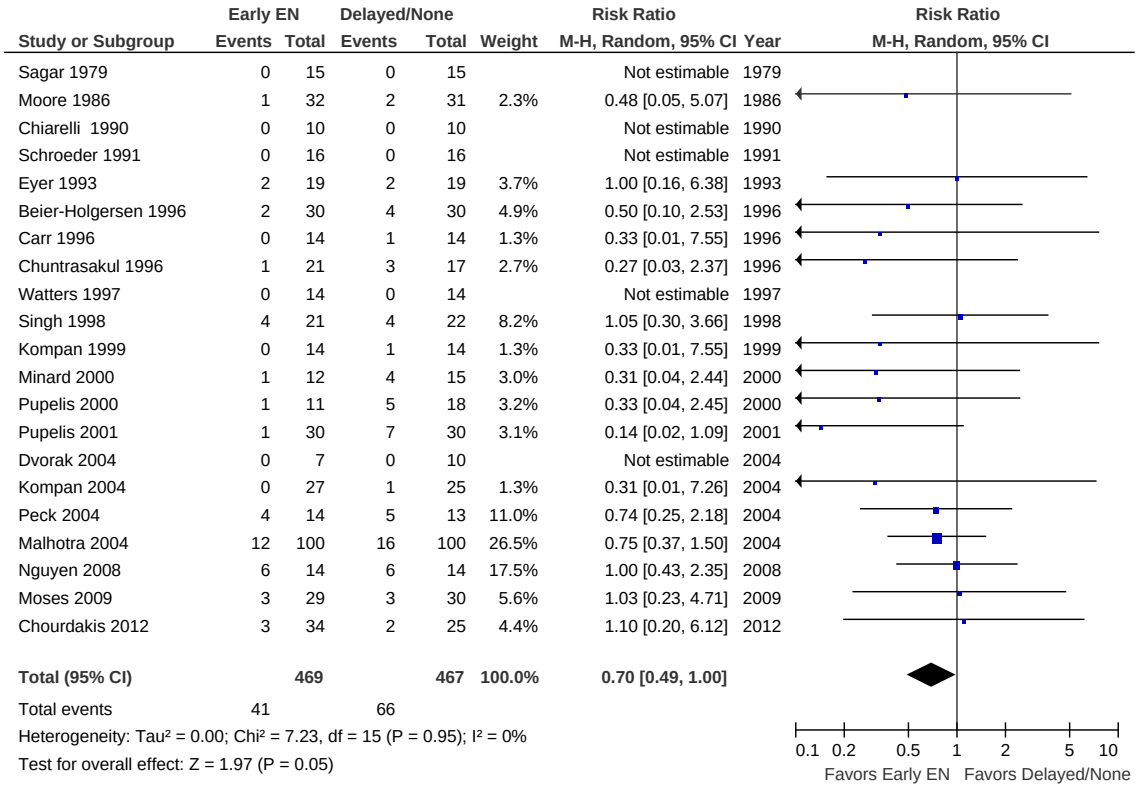
Bibliography: . Sagar, 1979; Moore 1986; Chiarelli 1990; Schroeder1991; Eyer 1993 Carr 1996; Chuntrasakul 1996; Watters, 1997 Beier-Holgersen 1996; Singh 1998; Kompan 1999; Minard 2000; Pupelis 2000; Pupelis 2001; Dvorak 2004; Malhotra 2004; Kompan 2004; Peck 2004]. Nguyen 2008;Moses 2009; Chaourdakis 2012

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With delayed nutrient intake	**With Early EN**		**Risk with delayed nutrient intake**	**Risk difference with Early EN** (95% CI)
Mortality (CRITICAL OUTCOME)											
966 (21 studies)	serious[1,2,3]	serious[4]	no serious indirectness	serious[5]	reporting bias strongly suspected[6]	**VERY LOW**[1,2,3,4,5,6] due to risk of bias, inconsistency, imprecision, publication bias	66/482 (13.7%)	41/484 (8.5%)	**RR 0.7** (0.49 to 1)	**137 per 1000**	**41 fewer per 1000** (from 70 fewer to 0 more)
Infectious Complications (CRITICAL OUTCOME)											
708	serious[1,2,3]	serious[4]	no serious	serious[7]	undetected		181/350	130/358	**RR 0.74**	**Study population**	

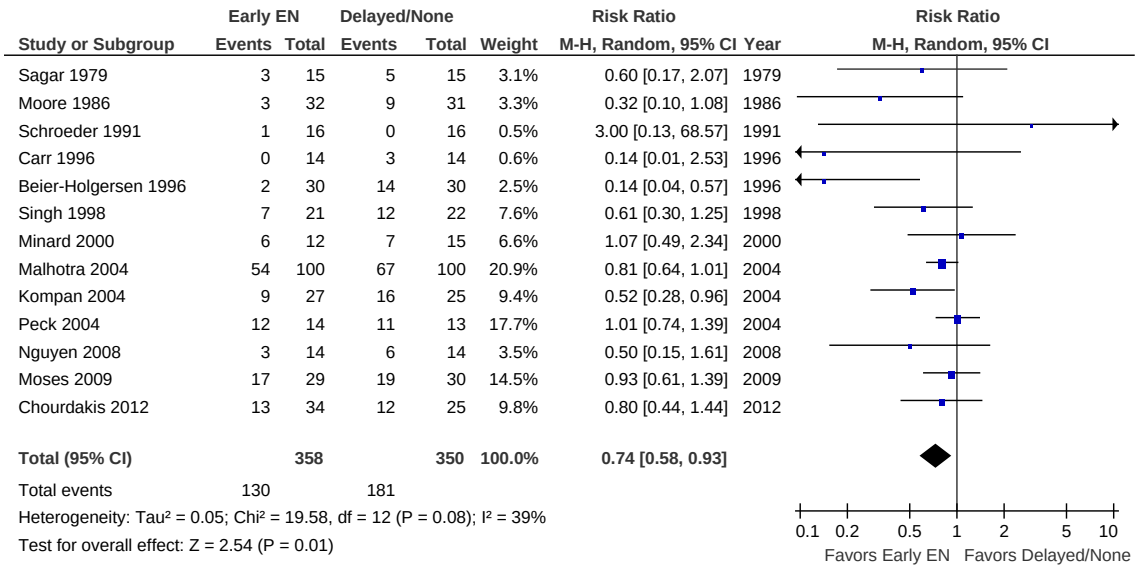
(13 studies)			indirectness			**VERY LOW**[1,2,3,4,] due to risk of bias, inconsistency, imprecision	(51.7%)	(36.3%)	(0.58 to 0.93)	**517 per 1000**	**134 fewer per 1000** (from 36 fewer to 217 fewer)

[1]Allocation concealment is only described well in 2/21 studies.
[2] Blinding is poorly described, it is a difficult intervention to blind.
[3] Intention to treat analysis was more likely to be done in recent studies than in earlier studies. In general, studies prior to 2000 were analyzed per protocol.
[4] Not all studies specifically looked at the effect of early vs. delayed EN on the outcome of mortality. One study reported primarily on cell-mediated immunity, while another was primarily done to look at nutritional outcomes.
[5] Only one of the studies has greater than 20% mortality in the control group. In general, the included studies have small number of subjects and small number of events (deaths)
[6] Small studies with large numbers of deaths are not seen in the published literature.
[7] Study size is the major source of imprecision. The smallest study included 27 subjects, while the largest included 200 subjects. The number of infections ranged from 0-67. There were various types of infections, blood stream, pneumonia, wound; this contributes to the imprecision of this estimate of the effect.
[8] Length of stay was rarely a primary outcome. Sample size was not necessarily large enough to detect a meaningful difference in this outcome.

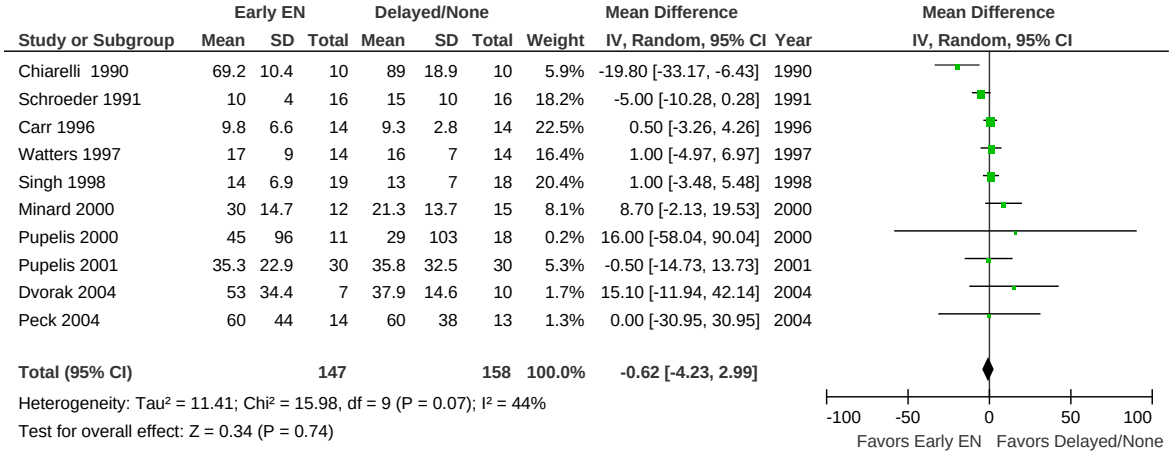
Outcome: Mortality



Outcome: Infections



Outcome Hospital LOS



Does the use of indirect calorimetry or predictive equations lead to improved clinical outcomes in critically ill adult patients?

Question: Indirect calorimetry vs predictive equations for

Bibliography: Saffle 1990; Singer 2011

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Predictive equations	**Indirect calorimetry**		**Risk with Predictive equations**	**Risk difference with Indirect calorimetry** (95% CI)
Hospital mortality											
161 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	29/79 (36.7%)	19/82 (23.2%)	**RR 0.63** (0.39 to 1.02)	**Study population**	
										367 per 1000	**136 fewer per 1000** (from 224 fewer to 7 more)
Hospital LOS (Better indicated by lower values)											
161 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	79	82	**-**		The mean hospital los in the intervention groups was **1.45 higher** (6.22 lower to 9.12 higher)

[1] Randomization unclear in one of two studies, ITT analysis used in one.

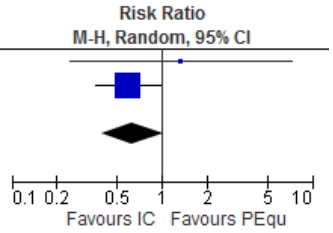
[2] Wide confidence interval.

Indirect Calorimetry vs. Predictive Equations, Outcome Mortality

Study or Subgroup	Indirect calorimetry Events	Total	Predictive equations Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Saffle	3	26	2	23	7.8%	1.33 [0.24, 7.26]	1990
Singer	16	56	27	56	92.2%	0.59 [0.36, 0.97]	2011
Total (95% CI)		**82**		**79**	**100.0%**	**0.63 [0.39, 1.02]**	
Total events	19		29				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.81$, df = 1 (P = 0.37); $I^2 = 0\%$

Test for overall effect: Z = 1.90 (P = 0.06)

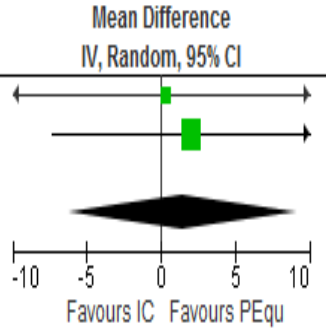


Indirect Calorimetry vs. Predictive Equations, Outcome Hospital Length of Stay

Study or Subgroup	Indirect calorimetry Mean	SD	Total	Predictive equations Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Saffle	48.8	22.9	26	48.5	24.9	23	32.5%	0.30 [-13.15, 13.75]	1990
Singer	33.8	22.9	56	31.8	27.3	56	67.5%	2.00 [-7.33, 11.33]	2011
Total (95% CI)			**82**			**79**	**100.0%**	**1.45 [-6.22, 9.12]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$

Test for overall effect: Z = 0.37 (P = 0.71)



Should. EN vs. IV fluids/NPO be used in critically ill patient?

Question: Should EN vs. IV fluids/NPO be used in critically ill patient?

Bibliography: Moore 1986; Chuntrasakul 1996; Singh 1998; Pupelis 2000; Pupelis 2001; Malhotra 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**A2. EN**	**IV fluids/NPO**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 13-89 days; assessed with: Deaths)												
5	randomized trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	20/215 (9.3%)	37/218 (17%)	RR 0.62 (0.37 to 1.05)	64 fewer per 1000 (from 107 fewer to 8 more)	LOW	CRITICAL
								28%[4]		106 fewer per 1000 (from 176 fewer to 14 more)		
Infectious complications (follow-up 21 days[5]; assessed with: infections)												
3	randomized trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[6]	none	64/153 (41.8%)	88/153 (57.5%)	RR 0.70 (0.48 to 1.02)	173 fewer per 1000 (from 299 fewer to 12 more)	LOW	CRITICAL
								67%[7]		201 fewer per 1000 (from 348 fewer to 13 more)		
ICU Length of Stay (follow-up 6-48 days; measured with: days ; Better indicated by lower values)												
3	randomized trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	62	65	-	MD 0.48 lower (3.74 lower to 2.79 higher)	LOW	CRITICAL
Hospital LOS (follow-up 13-103 days; measured with: days; Better indicated by lower values)												

3	randomized trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[8]	none	60	66	-	SMD 0.06 higher (0.29 lower to 0.41 higher)	LOW	CRITICAL

Ventilator days (follow-up 6-13 days; measured with: days; Better indicated by lower values)

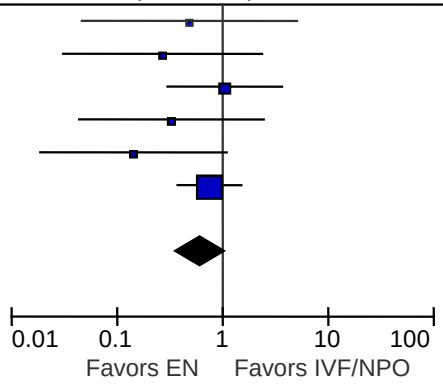
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A2. EN	IV fluids/NPO		Relative (95% CI)	Absolute	Quality	Importance
1	randomized trials	serious[1,2]	no serious inconsistency	no serious indirectness		serious[9] none	21	17	-	MD 0.83 lower (4.52 lower to 2.86 higher)		LOW	CRITICAL

[1] Allocation concealment is poorly described.
[2] Difficult to blind personnel and participants in the included studies, but it is not clear if outcome assessors were blinded.
[3] Wide confidence intervals are reported in most studies.
[4] The highest risk of mortality in a control group was 28% (Pupelis, 2001).
[5] Only one of the three studies reported length of stay. It was a maximum of 21 days in each group.
[6] There were relatively few subjects and few events in two of the three included studies.
[7] The highest risk of infection in a control group was 67% in Malhotra (2004).
[8] Only three studies reported on this outcome.
[9] Only one study reported on this outcome

EN vs. IV fluids/NPO, Outcome: Mortality

	EN		STD/NPO			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**	**M-H, Random, 95% CI**
Moore 1986	1	32	2	31	5.0%	0.48 [0.05, 5.07]	1986	
Chuntrasakul 1996	1	21	3	17	5.9%	0.27 [0.03, 2.37]	1996	
Singh 1998	4	21	4	22	17.8%	1.05 [0.30, 3.66]	1998	
Pupelis 2000	1	11	5	18	6.9%	0.33 [0.04, 2.45]	2000	
Pupelis 2001	1	30	7	30	6.7%	0.14 [0.02, 1.09]	2001	
Malhotra 2004	12	100	16	100	57.6%	0.75 [0.37, 1.50]	2004	
Total (95% CI)		**215**		**218**	**100.0%**	**0.62 [0.37, 1.05]**		
Total events	20		37					

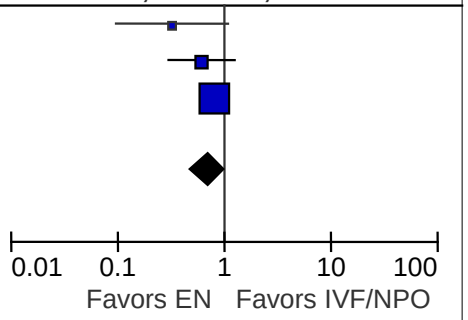
Heterogeneity: Tau² = 0.00; Chi² = 4.10, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.08)



EN vs. IV fluids/NPO, Outcome: Infections

Study or Subgroup	EN Events	EN Total	STD/NPO Events	STD/NPO Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moore 1986	3	32	9	31	8.7%	0.32 [0.10, 1.08]	1986
Singh 1998	7	21	12	22	21.3%	0.61 [0.30, 1.25]	1998
Malhotra 2004	54	100	67	100	69.9%	0.81 [0.64, 1.01]	2004
Total (95% CI)		**153**		**153**	**100.0%**	**0.70 [0.48, 1.02]**	
Total events	64		88				

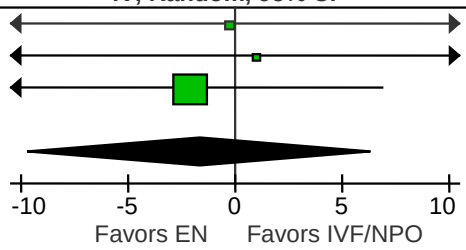
Heterogeneity: Tau² = 0.04; Chi² = 2.72, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 1.85 (P = 0.06)



EN vs. IV fluids/NPO, Outcome ICU LOS

Study or Subgroup	EN Mean	EN SD	EN Total	STD/NPO Mean	STD/NPO SD	STD/NPO Total	Weight	Mean Difference IV, Random, 95% CI
Chuntrasakul 1996	8.1	6.3	21	8.35	48	17	12.2%	-0.25 [-23.23, 22.73]
Pupelis 2000	7	41	11	6	34	18	7.7%	1.00 [-27.87, 29.87]
Pupelis 2001	13.9	14.6	30	16	20.4	30	80.0%	-2.10 [-11.08, 6.88]
Total (95% CI)			**62**			**65**	**100.0%**	**-1.63 [-9.67, 6.40]**

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

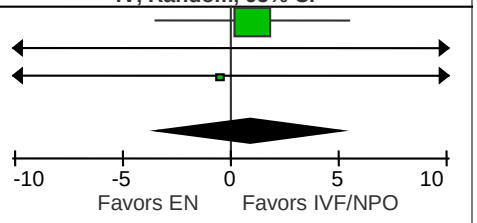


EN vs. IV fluids/NPO, Outcome Hospital LOS

Study or Subgroup	EN Mean	EN SD	EN Total	STD/NPO Mean	STD/NPO SD	STD/NPO Total	Weight	Mean Difference IV, Random, 95% CI	Year
Singh 1998	14	6.9	19	13	7	18	90.7%	1.00 [-3.48, 5.48]	1998
Pupelis 2000	45	96	11	29	103	18	0.3%	16.00 [-58.04, 90.04]	2000
Pupelis 2001	35.3	22.9	30	35.8	32.5	30	9.0%	-0.50 [-14.73, 13.73]	2001
Total (95% CI)			**60**			**66**	**100.0%**	**0.91 [-3.35, 5.18]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.42 (P = 0.67)



Should EN vs. PN be used in critically ill patients?

Question: EN vs. PN for the Critically Ill Adult

Bibliography: . Adams 1986; Borzetta 1994; Casas 2007; Cerra 1988; Chen 2011; Dunham 1994; Hadfield 1995; Kalfarentzos 1997; Kudsk 1992; Moore 1989; Peterson 1988; Rapp 1983; Woodcock 2001; Young 1987

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With PN	**With EN**		**Risk with PN**	**Risk difference with EN** (95% CI)
Mortality (CRITICAL OUTCOME)											
618 (12 studies)	serious[1,2,3]	serious[4,5]	no serious indirectness	serious[6]	undetected	**VERY LOW**[1,2,3,4,5,6] due to risk of bias, inconsistency, imprecision	47/304 (15.5%)	60/314 (19.1%)	**RR 1.25** (0.86 to 1.81)	**155 per 1000**	**39 more per 1000** (from 22 fewer to 125 more)
Infections (CRITICAL OUTCOME)											
496 (9 studies)	serious[1,2,4]	serious[4,7]	no serious indirectness	no serious imprecision	undetected	**LOW**[1,2,4,7] due to risk of bias, inconsistency	101/247 (40.9%)	53/249 (21.3%)	**RR 0.56** (0.39 to 0.79)	**409 per 1000**	**180 fewer per 1000** (from 86 more to 249 more)
Hospital LOS (CRITICAL OUTCOME; range of scores: 13-39; Better indicated by lower values)											

355 (6 studies)	serious[1,2]	serious[4]	no serious indirectness	serious[8]	undetected	**VERY LOW**[1,2,4,8] due to risk of bias, inconsistency, imprecision	171	184	-		The mean Hospital length of stay in the intervention groups was **0.35 lower** (1.76 lower to 1.05 higher)
ICU LOS (CRITICAL OUTCOME; Better indicated by lower values)											
180 (3 studies)	serious[1,2]	serious[8]	no serious indirectness	serious[8]	undetected	**VERY LOW**[1,2,8] due to risk of bias, inconsistency, imprecision	91	89	-		The mean ICU length of stay in the intervention groups was **0.82 lower** (1.29 to 0.34 lower)

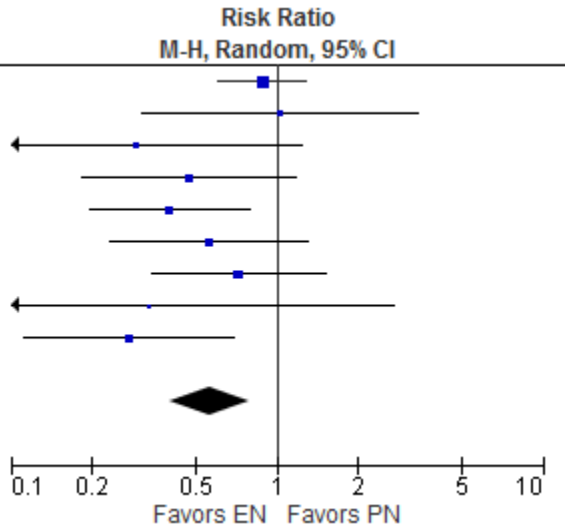
[1] 20% of the studies blinded participants, personnel, or outcome assessors.
[2] ~ 30% of the studies included all subjects randomized into treatment groups in their analyses.
[3] Only 75% of the included studies reported on Mortality as an outcome
[4] The subjects groups varied greatly between studies, brain injury, trauma with abdominal injury, subjects in ICU status post sepsis, pancreatitis, and elderly patients
[5] Sensitivity analysis was done to differentiate effects if PN kcals> > than EN or PN kcals were equivalent to EN.
[6] Small number of events and small sample sizes decrease the precision of the findings for this outcome.
[7] Infection type is not noted. Blood stream infection, pneumonia and or wound infection are included in this outcome
[8] Small sample size. Length of stay variables are confounded by early deaths that appear as shorter LOS, but not a desirable outcome.

EN vs. PN, Outcome: Infectious Complications

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams 1986	15	23	17	23	25.0%	0.88 [0.60, 1.30]	1986
Young 1987	5	28	4	23	6.9%	1.03 [0.31, 3.39]	1987
Peterson 1988	2	21	8	25	5.1%	0.30 [0.07, 1.25]	1988
Moore 1989	5	29	11	30	10.2%	0.47 [0.19, 1.19]	1989
Kudsk 1992	9	54	19	45	15.0%	0.39 [0.20, 0.78]	1992
Kalfarentzos 1997	5	18	10	20	11.2%	0.56 [0.23, 1.32]	1997
Woodcock 2001	6	16	11	21	13.5%	0.72 [0.34, 1.52]	2001
Casas 2007	1	11	3	11	2.6%	0.33 [0.04, 2.73]	2007
Chen 2011	5	49	18	49	10.5%	0.28 [0.11, 0.69]	2011
Total (95% CI)		**249**		**247**	**100.0%**	**0.56 [0.39, 0.79]**	
Total events	53		101				

Heterogeneity: Tau² = 0.09; Chi² = 12.10, df = 8 (P = 0.15); I² = 34%

Test for overall effect: Z = 3.26 (P = 0.001)

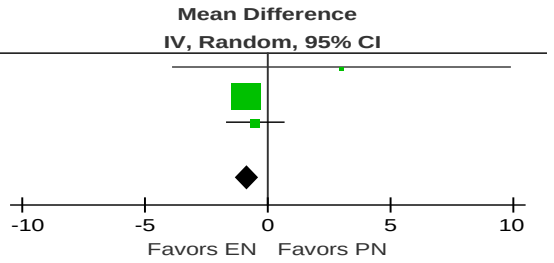


EN vs. PN, Outcome: ICU LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adams 1986	13	11	19	10	10	17	0.5%	3.00 [-3.86, 9.86]	1986
Peterson 1988	3.7	0.8	21	4.6	1	25	82.7%	-0.90 [-1.42, -0.38]	1988
Chen 2011	9.09	2.75	49	9.6	3.06	49	16.9%	-0.51 [-1.66, 0.64]	2011
Total (95% CI)			**89**			**91**	**100.0%**	**-0.82 [-1.29, -0.34]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 2 (P = 0.46); I² = 0%

Test for overall effect: Z = 3.38 (P = 0.0007)

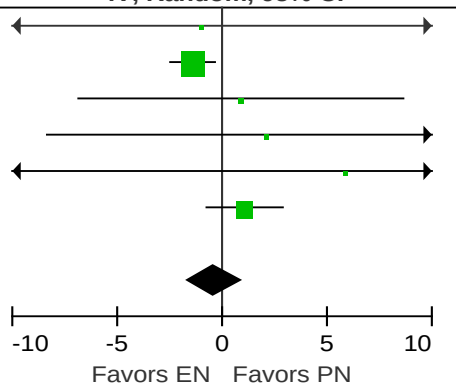


EN vs. PN, Outcome: Hospital LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adams 1986	30	21	19	31	29	17	0.7%	-1.00 [-17.71, 15.71]	1986
Peterson 1988	13.2	1.6	21	14.6	1.9	21	58.4%	-1.40 [-2.46, -0.34]	1988
Kudsk 1992	20.5	19.9	51	19.6	18.8	45	3.2%	0.90 [-6.85, 8.65]	1992
Borzetta 1994	39	23.1	28	36.9	14	21	1.8%	2.10 [-8.34, 12.54]	1994
Woodcock 2001	33.2	43	16	27.3	18.7	18	0.4%	5.90 [-16.87, 28.67]	2001
Chen 2011	23.32	5.6	49	22.24	3.27	49	35.5%	1.08 [-0.74, 2.90]	2011
Total (95% CI)			**184**			**171**	**100.0%**	**-0.35 [-1.76, 1.05]**	

Heterogeneity: Tau² = 0.58; Chi² = 6.12, df = 5 (P = 0.29); I² = 18%

Test for overall effect: Z = 0.49 (P = 0.62)

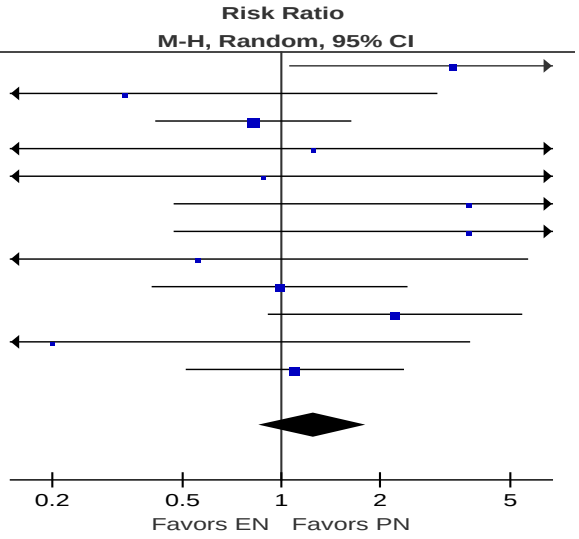


EN vs PN, Outcome: Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Rapp 1983	9	18	3	20	9.7%	3.33 [1.07, 10.43]	1983
Adams 1986	1	23	3	23	2.8%	0.33 [0.04, 2.97]	1986
Young 1987	10	28	10	23	23.4%	0.82 [0.42, 1.62]	1987
Cerra 1988	1	12	1	15	1.9%	1.25 [0.09, 17.98]	1988
Kudsk 1992	1	51	1	45	1.8%	0.88 [0.06, 13.70]	1992
Borzetta 1994	5	28	1	21	3.1%	3.75 [0.47, 29.75]	1994
Dunham 1994	5	28	1	21	3.1%	3.75 [0.47, 29.75]	1994
Hadfield 1995	1	18	2	20	2.5%	0.56 [0.05, 5.62]	1995
Kalfarentzos 1997	7	31	8	35	15.0%	0.99 [0.40, 2.41]	1997
Woodcock 2001	9	17	5	21	15.2%	2.22 [0.92, 5.40]	2001
Casas 2007	0	11	2	11	1.6%	0.20 [0.01, 3.74]	2007
Chen 2011	11	49	10	49	19.7%	1.10 [0.51, 2.35]	2011
Total (95% CI)		**314**		**304**	**100.0%**	**1.25 [0.86, 1.81]**	
Total events	60		47				

Heterogeneity: Tau² = 0.03; Chi² = 11.91, df = 11 (P = 0.37); I² = 8%

Test for overall effect: Z = 1.17 (P = 0.24)



Should EN be started early within the first 24-48 hours following admission?

Question: Should early vs. delayed EN be used for critically ill patients in the ICU?

Bibliography: Chiarelli 1990; Eyer 1993; Kompan 1999; Minard 2000; Dvorak 2004; Peck 2004; Nguyen 2008; Moses 2009 & Chourdakis 2012

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Delayed	**With Early**		**Risk with Delayed**	**Risk difference with Early** (95% CI)
Mortality (CRITICAL OUTCOME)											
355 (10 studies)	serious[1,2]	no serious inconsistency[3]	no serious indirectness	serious[4]	reporting bias strongly suspected[5]	**VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision, publication bias	24/175 (13.7%)	19/180 (10.6%)	**RR 0.83** (0.49 to 1.39)	**137 per 1000**	**23 fewer per 1000** (from 70 fewer to 53 more)
Infections (CRITICAL OUTCOME)											
272 (7 studies)	serious[1,2]	serious[6]	no serious indirectness	serious[4]	reporting bias strongly suspected[5]	**VERY LOW**[1,2,4,5,6] due to risk of bias, inconsistency, imprecision, publication bias	78/132 (59.1%)	63/140 (45%)	**OR 0.82** (0.64 to 1.05)	**591 per 1000**	**49 fewer per 1000** (from 111 fewer to 12 more)
ICU LOS (CRITICAL OUTCOME; range of scores: 14-40; Better indicated by lower values)											
231 (6 studies)	serious[1,2]	serious[7]	no serious indirectness	serious[4,8]	undetected	**VERY LOW**[1,2,4,7,8] due to risk of bias, inconsistency, imprecision	111	120	-		The mean icu los in the intervention groups was **0.06 lower** (3.92 lower to 3.81 higher)

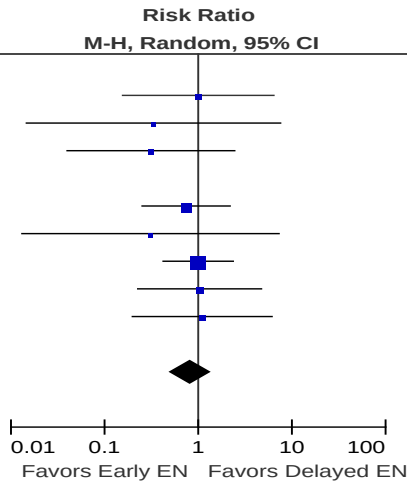
Ventilator days (CRITICAL OUTCOME; range of scores: 8.1-31.8; Better indicated by lower values)										
189 (6 studies)	serious[1,2]	serious[7]	no serious indirectness	serious	reporting bias strongly suspected[5]	**VERY LOW**[1,2,5,7] due to risk of bias, inconsistency, imprecision, publication bias	96	93	-		The mean ventilator days in the intervention groups was **2.11 higher** (0.95 lower to 5.16 higher)

[1] Blinding is difficult in this type of study, only two are reported to have blinded participants and or outcome assessors.
[2] Allocation concealment is poorly described, as it was not required to be reported when most of the studies were published. It is unclear if those who enrolled subjects knew to which group subjects would be assigned.
[3] The studies included subjects from many sub-populations of patients in ICU. Head injury, trauma, burn and post-op peritonitis are the various subject pools. Not downgrading for this measure of quality of evidence since this is the makeup of patients in ICUs
[4] Small sample sizes [range 7-34 subjects] and small numbers of deaths in each group.
[5] Studies that favored delayed EN are not included in the studies found and selected for this outcome.
[6] Various infections are counted, bacteremia, pneumonia, wound infection
[7] In measuring ICU LOS or ventilator days, it is uncertain if some subjects had decreased utilization d/t early mortality. Difficult to interpret.
[8] The outcome hospital length of stay is not a primary outcome. Do not know if enough subjects were enrolled to detect a difference in this outcome.

Early EN vs Standard, Outcome: Mortality

	Favors Early EN		Favors Delayed EN			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Chiarelli 1990	0	10	0	10		Not estimable	1990
Eyer 1993	2	19	2	19	7.8%	1.00 [0.16, 6.38]	1993
Kompan 1999	0	14	1	14	2.8%	0.33 [0.01, 7.55]	1999
Minard 2000	1	12	4	15	6.3%	0.31 [0.04, 2.44]	2000
Dvorak 2004	0	7	0	10		Not estimable	2004
Peck 2004	4	14	5	13	23.1%	0.74 [0.25, 2.18]	2004
Kompan 2004	0	27	1	25	2.7%	0.31 [0.01, 7.26]	2004
Nguyen 2008	6	14	6	14	36.6%	1.00 [0.43, 2.35]	2008
Moses 2009	3	29	3	30	11.6%	1.03 [0.23, 4.71]	2009
Chourdakis 2012	3	34	2	25	9.1%	1.10 [0.20, 6.12]	2012
Total (95% CI)		**180**		**175**	**100.0%**	**0.83 [0.49, 1.39]**	
Total events	19		24				

Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

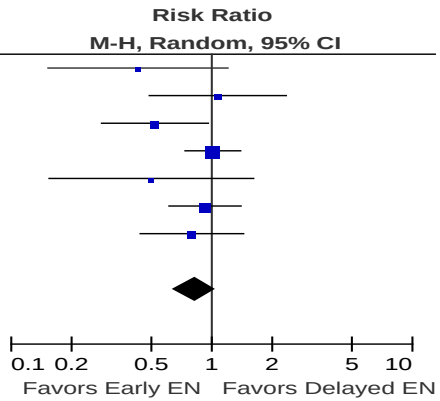


Early EN vs Standard, Outcome: Infectious Complication

	Favors Early EN		Favors Delayed EN			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Chiarelli 1990	3	10	7	10	5.3%	0.43 [0.15, 1.20]	1990
Minard 2000	6	12	7	15	8.7%	1.07 [0.49, 2.34]	2000
Kompan 2004	9	27	16	25	13.2%	0.52 [0.28, 0.96]	2004
Peck 2004	12	14	11	13	31.4%	1.01 [0.74, 1.39]	2004
Nguyen 2008	3	14	6	14	4.2%	0.50 [0.15, 1.61]	2008
Moses 2009	17	29	19	30	23.3%	0.93 [0.61, 1.39]	2009
Chourdakis 2012	13	34	12	25	13.8%	0.80 [0.44, 1.44]	2012
Total (95% CI)		**140**		**132**	**100.0%**	**0.82 [0.64, 1.05]**	
Total events	63		78				

Heterogeneity: Tau² = 0.03; Chi² = 7.80, df = 6 (P = 0.25); I² = 23%

Test for overall effect: Z = 1.58 (P = 0.11)

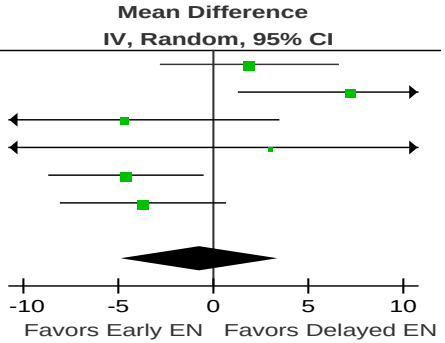


Early EN vs Standard, Outcome: ICU LOS

	Favors Early EN			Favors Delayed EN				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Eyer 1993	11.8	7.9	19	9.9	6.7	19	21.1%	1.90 [-2.76, 6.56]	1993
Minard 2000	18.5	8.8	12	11.3	6.1	15	18.2%	7.20 [1.34, 13.06]	2000
Kompan 2004	15.9	9.7	27	20.6	18.5	25	13.6%	-4.70 [-12.82, 3.42]	2004
Peck 2004	40	32	14	37	33	13	2.6%	3.00 [-21.55, 27.55]	2004
Nguyen 2008	11.3	3	14	15.9	7.1	14	22.6%	-4.60 [-8.64, -0.56]	2008
Chourdakis 2012	24.8	7.6	34	28.5	8.9	25	21.9%	-3.70 [-8.02, 0.62]	2012
Total (95% CI)			**120**			**111**	**100.0%**	**-0.70 [-4.83, 3.43]**	

Heterogeneity: Tau² = 15.41; Chi² = 14.43, df = 5 (P = 0.01); I² = 65%

Test for overall effect: Z = 0.33 (P = 0.74)

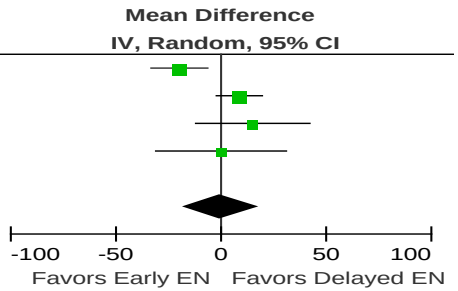


Early EN vs Standard, Outcome: Hospital LOS

	Favors Early EN			Favors Delayed EN				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Chiarelli 1990	69.2	10.4	10	89	18.9	10	30.3%	-19.80 [-33.17, -6.43]	1990
Minard 2000	30	14.7	12	21.3	13.7	15	32.1%	8.70 [-2.13, 19.53]	2000
Dvorak 2004	53	34.4	7	37.9	14.6	10	20.0%	15.10 [-11.94, 42.14]	2004
Peck 2004	60	44	14	60	38	13	17.6%	0.00 [-30.95, 30.95]	2004
Total (95% CI)			**43**			**48**	**100.0%**	**-0.18 [-18.24, 17.88]**	

Heterogeneity: Tau² = 233.93; Chi² = 12.04, df = 3 (P = 0.007); I² = 75%

Test for overall effect: Z = 0.02 (P = 0.98)

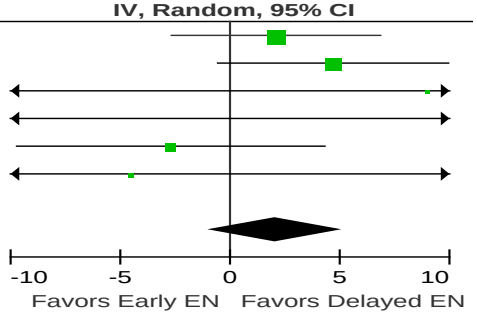


Early EN vs Standard, Outcome: Ventilator Days

	Favors Early EN			Favors Delayed EN				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Eyer 1993	10.2	8.1	19	8.1	6.8	19	41.3%	2.10 [-2.66, 6.86]	1993
Minard 2000	15.1	7.5	12	10.4	6.1	15	34.0%	4.70 [-0.55, 9.95]	2000
Kompan 2004	32	37	14	23	26	13	1.6%	9.00 [-14.99, 32.99]	2004
Peck 2004	31.8	35	7	20.9	14.4	10	1.2%	10.90 [-16.52, 38.32]	2004
Dvorak 2004	12.9	8.1	27	15.6	16.1	25	19.0%	-2.70 [-9.71, 4.31]	2004
Nguyen 2008	9.2	34	14	13.7	7.1	14	2.8%	-4.50 [-22.69, 13.69]	2008
Total (95% CI)			**93**			**96**	**100.0%**	**2.11 [-0.95, 5.16]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.96, df = 5 (P = 0.55); I² = 0%

Test for overall effect: Z = 1.35 (P = 0.18)



Does the level of infusion of EN (gastric versus small bowel) affect tolerance or risk of aspiration?

Question: Small Bowel vs Gastric for Critical Illness

Bibliography: Montecalvo 1992; Kortbeek 1999; Taylor 1999; Kearns 2000; Minard 2000; Day 2001; Esparza 2001; Boivin 2001; Newmann 2002; Davies 2002; Montejo 2002; Hsu 2009; White 2009; Acosta-Escribano 2010; Davies 2012

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Gastric	**With Small Bowel**		**Risk with Gastric**	**Risk difference with Small Bowel** (95% CI)
Pneumonia											
976 (12 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	153/494 (31%)	110/482 (22.8%)	**RR 0.75** (0.6 to 0.93)	**Study population**	
										310 per 1000	**77 fewer per 1000** (from 22 fewer to 124 fewer)
Mortality											
1186 (14 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	**MODERATE**[1] due to imprecision	147/607 (24.2%)	147/579 (25.4%)	**RR 1.03** (0.86 to 1.24)	**Study population**	
										242 per 1000	**7 more per 1000** (from 34 fewer to 58 more)
ICU LOS (Better indicated by lower values)											
895 (10 studies)	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	undetected	**LOW**[1,2] due to inconsistency, imprecision	458	437	**-**		The mean icu los in the intervention groups was **0.48 higher** (1.25 lower to 2.21 higher)
Hospital LOS (Better indicated by lower values)											

473 (5 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	undetected	**MODERATE**[1,3] due to imprecision	240	233	**-**		The mean hospital los in the intervention groups was **0.3 higher** (3.25 lower to 3.85 higher)
Duration of Ventilation (Better indicated by lower values)											
576 (6 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	**MODERATE**[1] due to imprecision	294	282	**-**		The mean duration of ventilation in the intervention groups was **0.36 lower** (2.02 lower to 1.3 higher)
Nutritional efficiency (Better indicated by lower values)											
689 (7 studies)	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[2] due to inconsistency	349	340	**-**		The mean nutritional efficiency in the intervention groups was **11.06 higher** (5.82 to 16.3 higher)
Pneumonia: VAP according to microbiology											
569 (6 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	95/291 (32.6%)	66/278 (23.7%)	**RR 0.72** (0.55 to 0.93)	**Study population**	
										326 per 1000	**91 fewer per 1000** (from 23 fewer to 147 fewer)

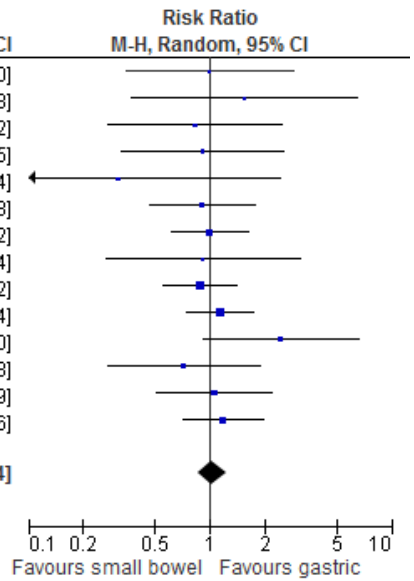
[1] Combined effect size crosses the line of no effect.
[2] Heterogeneitc with I2 > 50%
[3] Wide confidence intervals

Small Bowel vs. Gastric Feedings; Outcome: Mortality

Study or Subgroup	Small Bowel Events	Small Bowel Total	Gastric Events	Gastric Total	Weight	Risk Ratio M-H, Random, 95% CI
Montecalvo, 1992	5	19	5	19	3.1%	1.00 [0.35, 2.90]
Kortbeek, 1999	4	37	3	43	1.7%	1.55 [0.37, 6.48]
Taylor, 1999	5	41	6	41	2.9%	0.83 [0.28, 2.52]
Kearns, 2000	5	21	6	23	3.3%	0.91 [0.33, 2.55]
Minard, 2000	1	12	4	15	0.8%	0.31 [0.04, 2.44]
Esparaza, 2001	10	27	11	27	7.8%	0.91 [0.47, 1.78]
Boivin, 2001	18	39	18	39	15.3%	1.00 [0.62, 1.62]
Davies, 2002	4	34	5	39	2.3%	0.92 [0.27, 3.14]
Montejo, 2002	19	50	22	51	15.6%	0.88 [0.55, 1.42]
Hsu, 2009	26	59	24	62	19.4%	1.14 [0.74, 1.74]
White, 2010	11	51	5	57	3.6%	2.46 [0.92, 6.60]
Acosta-Escribano, 2010	6	50	9	54	3.8%	0.72 [0.28, 1.88]
Davies, 2012	13	91	12	89	6.6%	1.06 [0.51, 2.19]
Huang, 2012	20	48	17	48	13.6%	1.18 [0.71, 1.96]
Total (95% CI)		**579**		**607**	**100.0%**	**1.03 [0.86, 1.24]**
Total events	147		147			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.41$, $df = 13$ ($P = 0.93$); $I^2 = 0\%$

Test for overall effect: $Z = 0.33$ ($P = 0.74$)

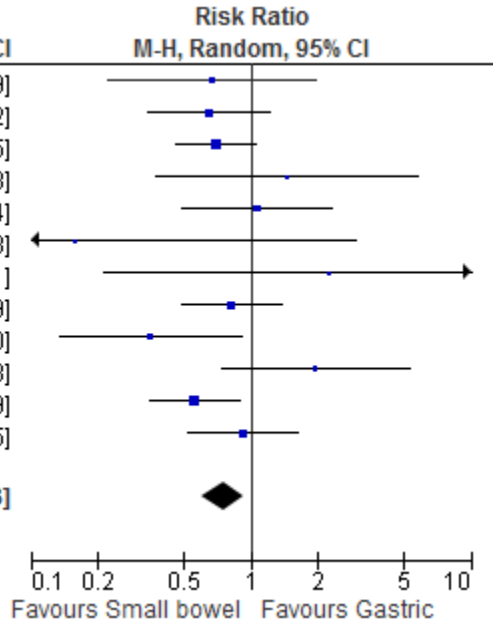


Small Bowel vs. Gastric Feedings, Outcome: Pneumonia

Study or Subgroup	Small Bowel Events	Small Bowel Total	Gastric Events	Gastric Total	Weight	Risk Ratio M-H, Random, 95% CI
Montecalvo, 1992	4	19	6	19	3.9%	0.67 [0.22, 1.99]
Kortbeek, 1999	10	37	18	43	10.4%	0.65 [0.34, 1.22]
Taylor, 1999	18	41	26	41	20.6%	0.69 [0.46, 1.05]
Kearns, 2000	4	21	3	23	2.5%	1.46 [0.37, 5.78]
Minard, 2000	6	12	7	15	7.2%	1.07 [0.49, 2.34]
Day, 2001	0	14	2	11	0.6%	0.16 [0.01, 3.03]
Davies, 2002	2	31	1	35	0.9%	2.26 [0.22, 23.71]
Montejo, 2002	16	50	20	51	14.2%	0.82 [0.48, 1.39]
Hsu, 2009	5	59	15	62	5.1%	0.35 [0.14, 0.90]
White, 2010	11	57	5	51	4.7%	1.97 [0.73, 5.28]
Acosta-Escribano, 2010	16	50	31	54	17.5%	0.56 [0.35, 0.89]
Davies, 2012	18	91	19	89	12.4%	0.93 [0.52, 1.65]
Total (95% CI)		**482**		**494**	**100.0%**	**0.75 [0.60, 0.93]**
Total events	110		153			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.33$, df = 11 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 2.56 (P = 0.01)

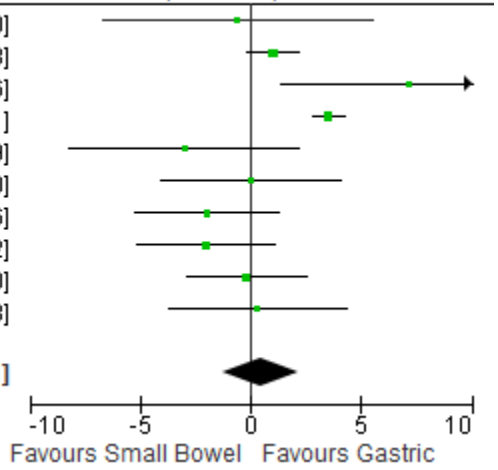


Small Bowel vs. Gastric Feedings, Outcome: ICU LOS

Study or Subgroup	Small Bowel Mean	SD	Total	Gastric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Montecalvo, 1992	11.7	8.2	19	12.3	10.8	19	5.4%	-0.60 [-6.70, 5.50]
Kearns, 2000	17	2	21	16	2	23	15.4%	1.00 [-0.18, 2.18]
Minard, 2000	18.5	8.8	12	11.3	6.1	15	5.7%	7.20 [1.34, 13.06]
Davies, 2002	13.9	1.8	34	10.4	1.2	39	16.2%	3.50 [2.79, 4.21]
Montejo, 2002	15	10	50	18	16	51	6.7%	-3.00 [-8.19, 2.19]
Hsu, 2009	18.2	11.8	59	18.2	11.2	62	8.6%	0.00 [-4.10, 4.10]
White, 2010	7.12	6	51	9.1	10.55	55	10.5%	-1.98 [-5.22, 1.26]
Acosta-Escribano, 2010	16	9	50	18	7	54	10.8%	-2.00 [-5.12, 1.12]
Davies, 2012	12.5	8.6	91	12.7	9.8	89	11.9%	-0.20 [-2.90, 2.50]
Huang, 2012	17.2	11.4	50	16.9	9.1	51	8.8%	0.30 [-3.73, 4.33]
Total (95% CI)			**437**			**458**	**100.0%**	**0.48 [-1.25, 2.21]**

Heterogeneity: $Tau^2 = 4.69$; $Chi^2 = 42.54$, df = 9 ($P < 0.00001$); $I^2 = 79\%$

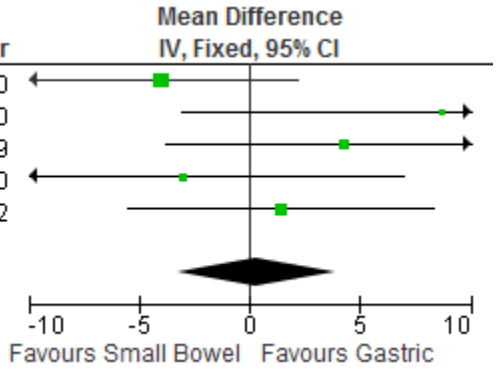
Test for overall effect: $Z = 0.54$ ($P = 0.59$)



Small Bowel vs. Gastric Feedings, Outcome: Hospital LOS

Study or Subgroup	Small Bowel Mean	SD	Total	Gastric Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Kearns, 2000	39	10	21	43	11	23	32.8%	-4.00 [-10.21, 2.21]	2000
Minard, 2000	30	14.7	12	21.3	14.7	12	9.1%	8.70 [-3.06, 20.46]	2000
Hsu, 2009	36	24.2	59	31.7	21.1	62	19.2%	4.30 [-3.81, 12.41]	2009
Acosta-Escribano, 2010	38	24	50	41	28	54	12.6%	-3.00 [-13.00, 7.00]	2010
Davies, 2012	28.8	26.1	91	27.4	21.1	89	26.3%	1.40 [-5.53, 8.33]	2012
Total (95% CI)			**233**			**240**	**100.0%**	**0.30 [-3.25, 3.85]**	

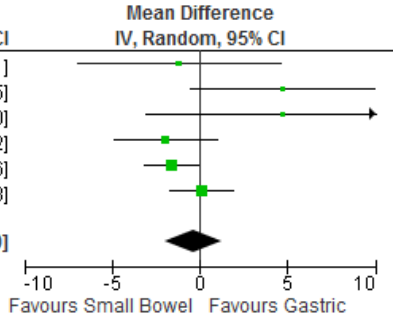
Heterogeneity: Chi² = 5.25, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 0.16 (P = 0.87)



Small Bowel vs. Gastric Feedings, Outcome: Days of Ventilation

Study or Subgroup	Small Bowel Mean	SD	Total	Gastric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Montecalvo, 1992	10.2	7.1	19	11.4	10.8	19	6.9%	-1.20 [-7.01, 4.61]
Minard, 2000	15.1	7.5	12	10.4	6.1	15	8.2%	4.70 [-0.55, 9.95]
Hsu, 2009	28.5	24.9	59	23.8	18.2	62	4.1%	4.70 [-3.10, 12.50]
White, 2010	5.73	5.29	51	7.68	9.81	55	18.5%	-1.95 [-4.92, 1.02]
Acosta-Escribano, 2010	7.3	4	50	8.9	4	54	32.8%	-1.60 [-3.14, -0.06]
Davies, 2012	9.8	6.2	91	9.7	6.3	89	29.4%	0.10 [-1.73, 1.93]
Total (95% CI)			**282**			**294**	**100.0%**	**-0.36 [-2.02, 1.30]**

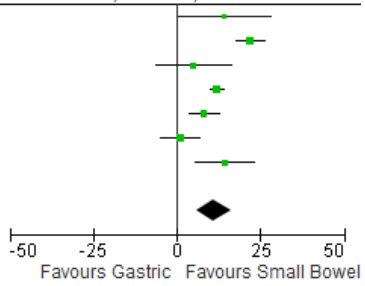
Heterogeneity: Tau² = 1.57; Chi² = 8.67, df = 5 (P = 0.12); I² = 42%
Test for overall effect: Z = 0.43 (P = 0.67)



Small Bowel vs. Gastric Feedings, Outcome: Nutritional Efficiency

Study or Subgroup	Small Bowel Mean	SD	Total	Gastric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Montecalvo, 1992	61	17	19	46.9	25.9	19	8.2%	14.10 [0.17, 28.03]	1992
Kearns, 2000	69	7	21	47	7	23	17.4%	22.00 [17.86, 26.14]	2000
Montejo, 2002	80	28	50	75	30	51	10.2%	5.00 [-6.31, 16.31]	2002
Hsu, 2009	95	5	59	83	6	62	19.0%	12.00 [10.04, 13.96]	2009
Acosta-Escribano, 2010	92	7	50	84	15	54	17.1%	8.00 [3.55, 12.45]	2010
Davies, 2012	72	21	91	71	19	89	15.7%	1.00 [-4.85, 6.85]	2012
Huang, 2012	90.4	20.5	50	76.2	24.9	51	12.5%	14.20 [5.31, 23.09]	2012
Total (95% CI)			**340**			**349**	**100.0%**	**11.06 [5.82, 16.30]**	

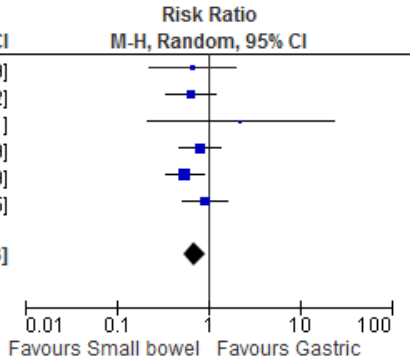
Heterogeneity: Tau² = 36.70; Chi² = 40.88, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 4.14 (P < 0.0001)



Small Bowel vs. Gastric Feedings, Outcome: Pneumonia, VAP by Micro

Study or Subgroup	Small Bowel Events	Total	Gastric Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Montecalvo, 1992	4	19	6	19	5.7%	0.67 [0.22, 1.99]
Kortbeek, 1999	10	37	18	43	16.8%	0.65 [0.34, 1.22]
Davies, 2002	2	31	1	35	1.2%	2.26 [0.22, 23.71]
Montejo, 2002	16	50	20	51	24.3%	0.82 [0.48, 1.39]
Acosta-Escribano, 2010	16	50	31	54	31.4%	0.56 [0.35, 0.89]
Davies, 2012	18	91	19	89	20.6%	0.93 [0.52, 1.65]
Total (95% CI)		**278**		**291**	**100.0%**	**0.72 [0.55, 0.93]**
Total events	66		95			

Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)



Does the use of trophic EN improve outcomes in patients diagnosed with ALI/ARDS? In patients at moderate risk with ALI/ARDS, trophic feeds should be considered.

Question: Trophic feeds versus full feeds in critically ill patients with Acute Lung Injury

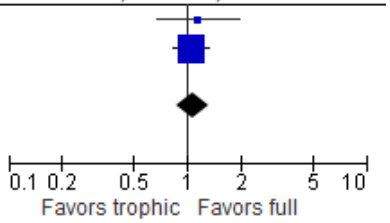
Bibliography: 3.3a Trophic feeds vs. full feeds in ALI: Rice 2011; Rice 2012

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Trophic feeds versus full feeds in critically ill patients**		**Risk with Control**	**Risk difference with Trophic feeds versus full feeds in critically ill patients** (95% CI)
Mortality											
1190 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	129/584 (22.1%)	140/606 (23.1%)	**RR 1.04** (0.85 to 1.29)	**Study population**	
										221 per 1000	**9 more per 1000** (from 33 fewer to 64 more)
Ventilator associated pneumonia											
1200 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	51/594 (8.6%)	51/606 (8.4%)	**RR 0.98** (0.68 to 1.43)	**Study population**	
										86 per 1000	**2 fewer per 1000** (from 27 fewer to 37 more)

Full vs. Trophic Feeds, Outcome Mortality

Study or Subgroup	Trophic Events	Trophic Total	Full Events	Full Total	Weight	Risk Ratio M-H, Random, 95% CI
Rice 2011	22	98	20	102	15.3%	1.14 [0.67, 1.96]
Rice 2012	118	508	109	492	84.7%	1.05 [0.83, 1.32]
Total (95% CI)		**606**		**594**	**100.0%**	**1.06 [0.86, 1.31]**
Total events	140		129			

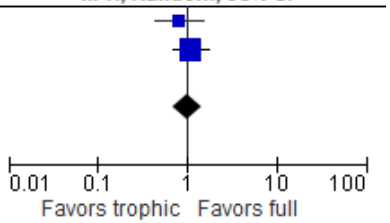
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)



Full vs Trophic Feeds, Outcome VAP

Study or Subgroup	Trophic Events	Trophic Total	Full Events	Full Total	Weight	Risk Ratio M-H, Random, 95% CI
Rice 2011	14	98	18	102	33.3%	0.81 [0.43, 1.54]
Rice 2012	37	508	33	492	66.7%	1.09 [0.69, 1.71]
Total (95% CI)		**606**		**594**	**100.0%**	**0.98 [0.68, 1.43]**
Total events	51		51			

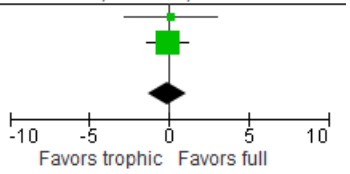
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)



Full vs Trophic Feeds, Outcome Ventilator-free Days

Study or Subgroup	Trophic Mean	Trophic SD	Trophic Total	Full Mean	Full SD	Full Total	Weight	Mean Difference IV, Random, 95% CI
Rice 2011	17.9	10.4	98	17.8	10.5	102	17.7%	0.10 [-2.80, 3.00]
Rice 2012	14.9	11.4722	508	15	10.1603	492	82.3%	-0.10 [-1.44, 1.24]
Total (95% CI)			**606**			**594**	**100.0%**	**-0.06 [-1.28, 1.15]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



Protein Dose

Question: High protein vs. Low protein for Critical Illness

Bibliography: . Clifton 1985 and Scheinkestel 2003

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Low protein	**With High protein**		**Risk with Low protein**	**Risk difference with High protein** (95% CI)
Mortality (CRITICAL OUTCOME)											
70 (2 studies) 1 months	serious[1,2]	serious[3]	no serious indirectness	serious[4]	undetected	**VERY LOW**[1,2,3,4] due to risk of bias, inconsistency, imprecision	5/20 (25%)	10/50 (20%)	**RR 0.6** (0.25 to 1.47)	**Study population**	
										250 per 1000	**100 fewer per 1000** (from 188 fewer to 118 more)
										Moderate	
										250 per 1000	**100 fewer per 1000** (from 188 fewer to 118 more)

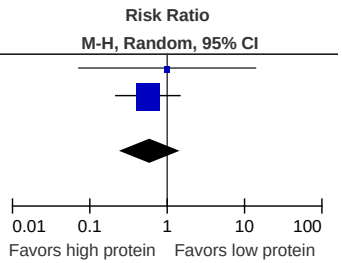
[1] Study personnel were not blinded
[2] Allocation concealment is not clear.
[3] Small number of subjects in both studies..
[4] Confidence intervals are wide

High protein EN only vs. Low protein EN only, Outcome: Mortality

	High protein		Low protein			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	11.6%	1.00 [0.07, 13.87]	1985
Scheinkestel 2003	9	40	4	10	88.4%	0.56 [0.22, 1.46]	2003
Total (95% CI)		**50**		**20**	**100.0%**	**0.60 [0.25, 1.47]**	
Total events	10		5				

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)

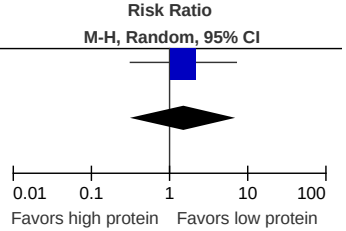


High protein EN only vs. Low protein EN only, Outcome: Infection

	High protein		Low protein			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Clifton 1985	3	10	2	10	100.0%	1.50 [0.32, 7.14]	1985
Total (95% CI)		**10**		**10**	**100.0%**	**1.50 [0.32, 7.14]**	
Total events	3		2				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.51 (P = 0.61)



Should GRVs be used as a marker for aspiration to monitor ICU patients on EN?

Question: Should High vs Low Gastric Residual Volume be used for Critical Illness?

Bibliography: Montejo 2010 Reignier 2013

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With High vs Low Gastric Residual Volume**		**Risk with Control**	**Risk difference with High vs Low Gastric Residual Volume** (95% CI)
Mortality											
771 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	87/387 (22.5%)	94/384 (24.5%)	**RR 1.08** (0.84 to 1.39)	**Study population**	
										225 per 1000	**18 more per 1000** (from 36 fewer to 88 more)

[1] The studies were not blinded, and one did not use ITT analysis.

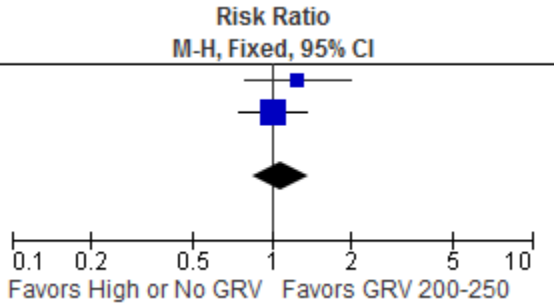
[2] The combined effect size crosses the line of no effect.

Outcome Mortality

Study or Subgroup	High or No GRV Events	Total	GRV 200-250 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Montejo 2010	31	157	26	165	29.1%	1.25 [0.78, 2.01]
Reignier 2013	63	227	61	222	70.9%	1.01 [0.75, 1.36]
Total (95% CI)		**384**		**387**	**100.0%**	**1.08 [0.84, 1.39]**
Total events	94		87			

Heterogeneity: $Chi^2 = 0.57$, $df = 1$ ($P = 0.45$); $I^2 = 0\%$

Test for overall effect: $Z = 0.60$ ($P = 0.55$)



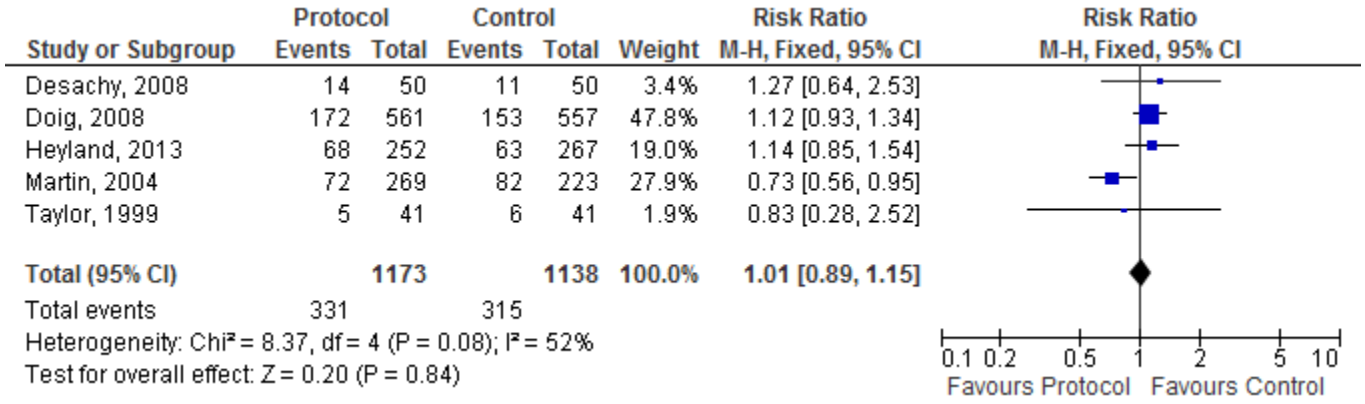
Should EN feeding protocols be used in the adult ICU setting?

Question: Nutritional Adequacy for Critical Illness											
Quality assessment							**Summary of Findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Nutritional Adequacy**		**Risk with Control**	**Risk difference with Nutritional Adequacy** (95% CI)
Mortality											
2311 (5 studies)	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to inconsistency, imprecision	315/1138 (27.7%)	331/1173 (28.2%)	**RR 1.01** (0.89 to 1.15)	**Study population**	
										277 per 1000	**3 more per 1000** (from 30 fewer to 42 more)
ICU LOS (Better indicated by lower values)											
1737 (3 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	**MODERATE**[2] due to imprecision	874	863	-		The mean icu los in the intervention groups was **0.63 lower** (2.07 lower to 0.81 higher)
Infections											
701 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	61/408 (15%)	32/293 (10.9%)	**RR 0.59** (0.43 to 0.81)	**Study population**	
										150 per 1000	**61 fewer per 1000** (from 28 fewer to 85 fewer)
Hospital LOS (Better indicated by lower values)											

1737 (3 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	**MODERATE**[2] due to imprecision	874	863	-	The mean hospital los in the intervention groups was **0.03 lower** (3.29 lower to 3.23 higher)
Nutritional Efficacy (Better indicated by lower values)										
519 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[3] due to risk of bias	267	252	-	The mean nutritional efficacy in the intervention groups was **10.3 higher** (4.89 to 15.71 higher)

[1] Varied protocols tested
[2] The estimate of effect for all studies crosses the line of no effect.
[3] Single study

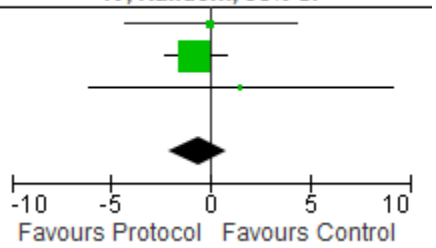
Feeding Protocol vs. Control, Outcome: Mortality



Feeding Protocol vs. Control, Outcome: ICU LOS

	Protocol			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Desachy, 2008	15	11	50	15	11	50	11.1%	0.00 [-4.31, 4.31]	
Doig, 2008	9.1	12.0585	561	9.9	14.4183	557	85.3%	-0.80 [-2.36, 0.76]	
Heyland, 2013	7.2	37.1715	252	5.7	50.624	267	3.6%	1.50 [-6.11, 9.11]	
Total (95% CI)			**863**			**874**	**100.0%**	**-0.63 [-2.07, 0.81]**	

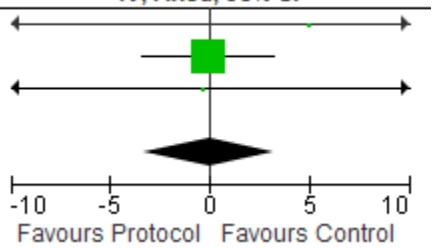
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



Feeding Protocol vs. Control, Outcome: Hospital LOS

	Protocol			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Desachy, 2008	56	59	50	51	75	50	1.5%	5.00 [-21.45, 31.45]	
Doig, 2008	24.2	31.3521	561	24.3	25.232	557	95.7%	-0.10 [-3.43, 3.23]	
Heyland, 2013	13.5	120.099	252	13.8	106.2275	267	2.8%	-0.30 [-19.85, 19.25]	
Total (95% CI)			**863**			**874**	**100.0%**	**-0.03 [-3.29, 3.23]**	

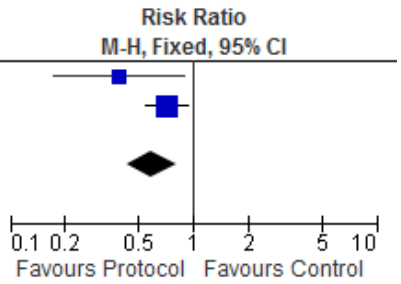
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)



Feeding Protocol vs. Control, Outcome: Infections

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heyland, 2013	7	252	26	367	37.7%	0.39 [0.17, 0.89]
Taylor, 1999	25	41	35	41	62.3%	0.71 [0.54, 0.94]
Total (95% CI)		**293**		**408**	**100.0%**	**0.59 [0.43, 0.81]**
Total events	32		61			

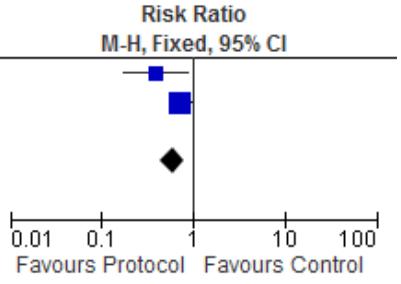
Heterogeneity: Chi² = 2.73, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 3.26 (P = 0.001)



Feeding Protocol vs Standard, Outcome: Infections

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heyland, 2013	7	252	26	367	37.7%	0.39 [0.17, 0.89]
Taylor, 1999	25	41	35	41	62.3%	0.71 [0.54, 0.94]
Total (95% CI)		**293**		**408**	**100.0%**	**0.59 [0.43, 0.81]**
Total events	32		61			

Heterogeneity: Chi² = 2.73, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 3.26 (P = 0.001)



Should Motility Agents be used Routinely?

Question: Motility agent vs. Control for Patients at Risk of Aspiration

Bibliography: Yavagal 2000, Berne 2002, Meissner 2003 , Boivin 2001, Chapman 2000, Nguyen 2007, Nursal 2007, and Reignier 2002

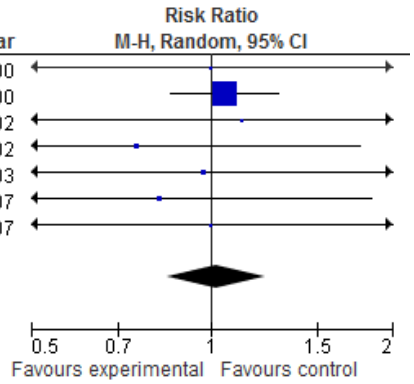
Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Motility agent**		**Risk with Control**	**Risk difference with Motility agent** (95% CI)
Mortality											
609 (7 studies)	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[2,3]	undetected	**LOW**[1,2] due to risk of bias, imprecision	124/331 (37.5%)	100/278 (36%)	**RR 1.02** (0.84 to 1.23)	**Study population**	
										375 per 1000	**7 more per 1000** (from 60 fewer to 86 more)
Infection (pneumonia)											
454 (3 studies)	serious[1]	no serious inconsistency	serious	Serious[3]	undetected	**LOW**[1] due to risk of bias, indirectness	66/253 (26.1%)	48/201 (23.9%)	**RR 0.84** (0.57 to 1.25)	**Study population**	
										261 per 1000	**42 fewer per 1000** (from 112 fewer to 65 more)
Length of Stay Location not specified (Better indicated by lower values)											
19 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	9	10	**-**		The mean length of stay location not specified in the intervention groups was **1.2 lower** (10.04 lower to 7.64 higher)

[1] Intent to treat analysis was used in less than half the trials.
[2] The CI are very wide, suggesting imprecision
[3]The combined effect size crosses the line of no effect.

Motility Agent vs. Control, Outcome Mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chapman 2000	2	10	2	10	1.1%	1.00 [0.17, 5.77]	2000
Yavagal 2000	73	131	92	174	82.2%	1.05 [0.86, 1.30]	2000
Berne 2002 (1)	2	32	2	36	1.0%	1.13 [0.17, 7.53]	2002
Reignier 2002 (2)	6	20	8	20	4.8%	0.75 [0.32, 1.77]	2002
Meissner 2003	6	38	7	43	3.5%	0.97 [0.36, 2.63]	2003
Nguyen 2007	8	37	10	38	5.4%	0.82 [0.36, 1.85]	2007
Nursal 2007	3	10	3	10	2.0%	1.00 [0.26, 3.81]	2007
Total (95% CI)		**278**		**331**	**100.0%**	**1.02 [0.84, 1.23]**	
Total events	100		124				

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 6 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

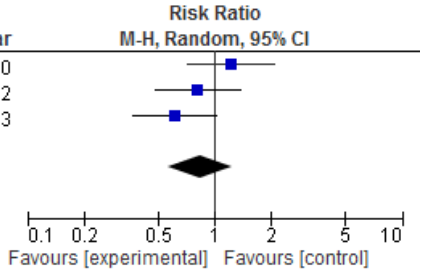


(1) N
(2) Chapman 2000 and McClaren 2008 excluded, no deaths

Motility Agent vs. Control, Outcome Pneumonia

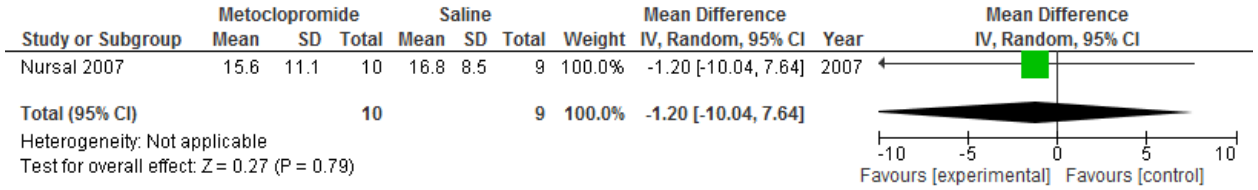
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Yavagal 2000	22	131	24	174	32.9%	1.22 [0.72, 2.07]	2000
Berne 2002	13	32	18	36	33.0%	0.81 [0.48, 1.38]	2002
Meissner 2003 (1)	13	38	24	43	34.2%	0.61 [0.37, 1.03]	2003
Total (95% CI)		**201**		**253**	**100.0%**	**0.84 [0.57, 1.25]**	
Total events	48		66				

Heterogeneity: Tau² = 0.05; Chi² = 3.40, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.85 (P = 0.40)



(1) Unknown safety and efficacy of the agent used in the Meissner 2003 study, naloxone.

Motility Agent vs. Control, Outcome: LOS



Should a combination (Erythro 200 mg + Metoclopramide 10 mg) vs monotherapy (Erythro 200 mg) be used for patients at risk for aspiration

Bibliography: Nguyen 2007											
Quality assessment							**Summary of Findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Monotherapy (Erythro 200 mg)	**With Combination (Erythro 200 mg + Metoclopromide 10mg)**		**Risk with Monotherapy (Erythro 200 mg)**	**Risk difference with Combination (Erythro 200 mg + Metoclopromide 10mg)** (95% CI)
Mortality											
75 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	10/38 (26.3%)	8/37 (21.6%)	**RR 0.82** (0.36 to 1.85)	**Study population**	
										263 per 1000	**47 fewer per 1000** (from 168 fewer to 224 more)
Hospital Length of Stay (Better indicated by lower values)											

75 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	38	37	**-**		The mean hospital length of stay in the intervention groups was **5.2 higher** (1.7 to 8.7 higher)
Failure of feeding day (Better indicated by higher values)											
75 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	38	37	**-**		The mean failure of feeding day in the intervention groups was **2 higher** (1.77 to 2.23 higher)
Need for post pyloric feeds											
75 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	8/38 (21.1%)	2/37 (5.4%)	**RR 0.26** (0.06 to 1.13)	**Study population**	
										211 per 1000	**156 fewer per 1000** (from 198 fewer to 27 more)
Diarrhea Incidence											
75 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**HIGH**	10/38 (26.3%)	20/37 (54.1%)	**OR 3.29** (1.25 to 8.68)	**Study population**	
										263 per 1000	**277 more per 1000** (from 45 more to 493 more)

[1] Blinding and/or ITT analysis only used in half the studies
[2] Combined effect size crosses the line of no effect.

Should immune modulation formula versus standard formula be used in critically ill patients?

Diets with arginine and other vs. standard

Bibliography: Atkinson 1998; Beale 2008; Bower, 1994; Caparros 2001; Cerra 1991; Chuntrasakul 2003; Canejero 2002; Engel 1997; Galban 2000; Gottschlich 1990; Kieft 2005; Kudsk 1996; Kuhls 2007; Mendez 1997; Moore 1994; Pearce 2006; Rodrigo 1997; Tsuei 2004; Weimann 1998 & Wibbenbeyer 2006

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With standard	**With Diets with arginine and other**		**Risk with standard**	**Risk difference with Diets with arginine and other** (95% CI)
Mortality (w/ quality sub-analysis) (CRITICAL OUTCOME)											
2343 (21 studies)	serious[1]	serious[2,3]	no serious indirectness	serious[4]	undetected	**VERY LOW**[1,2,3,4] due to risk of bias, inconsistency, imprecision	299/1135 (26.3%)	322/1208 (26.7%)	**RR 1.03** (0.91 to 1.17)	**263 per 1000**	**8 more per 1000** (from 24 fewer to 45 more)
Infectious complications (w/ quality sub-analyses) (CRITICAL OUTCOME)											
1606 (12 studies)	serious[1]	serious[2,3,5]	serious[6]	serious[7]	undetected	**VERY LOW**[1,2,3,5,6,7] due to risk of bias, inconsistency, indirectness, imprecision	365/773 (47.2%)	385/833 (46.2%)	**RR 0.98** (0.81 to 1.18)	**472 per 1000**	**9 fewer per 1000** (from 90 fewer to 85 more)

Hospital Length of Stay (CRITICAL OUTCOME; Better indicated by lower values)											
1099 (12 studies)	serious[1]	serious[2,3,8]	no serious indirectness	serious[9,10,11]	undetected	**VERY LOW**[1,2,3,8,9,10,11] due to risk of bias, inconsistency, imprecision	538	561	-		The mean hospital length of stay in the intervention groups was **0.93 lower** (5.75 lower to 3.89 higher)
Ventilated Days (CRITICAL OUTCOME; Better indicated by lower values)											
818 (9 studies)	serious[1]	serious[2,3]	no serious indirectness	serious[9,11]	undetected	**VERY LOW**[1,2,3,9,11] due to risk of bias, inconsistency, imprecision	403	415	-		The mean ventilated days in the intervention groups was **1.43 lower** (2.92 lower to 0.06 higher)

[1] In studies published prior to 2000, reporting biases such as concealing the allocation of subjects or assuring subjects all subjects randomized are included in the analysis was not clearly reported. More than half the studies in this review were published =/< 2000.

[2] The populations from which the subjects in the included studies varies, and includes trauma, burn, critically ill and septic subjects. Since these groups reflect the population of an ICU, did not down grade for this

[3] Two different formula were study formula (Immun-Aid and Impact) and control formula varied form "standard" to high protein formula to elemental formula. Downgraded for this inconsistency across studies.

[4] Confidence intervals are very wide for the included studies. Sub-analysis looking at only studies with > 50 subjects did not change the estimate of the effect.

[5] The I^2 statistic for the outcome Infectious Complications is 66%. Desired value is < 50%

[6] Uncertain of specific infection, central line infection vs. pneumonia vs. wound infection.

[7] Confidence intervals the smaller studies are very wide. Removing the studies with less than 50 total subjects did not change the estimate of the effect, it still crossed the line of no effect. Studies done more recently have narrower confidence intervals, but still a difference is not seen between the experimental groups.

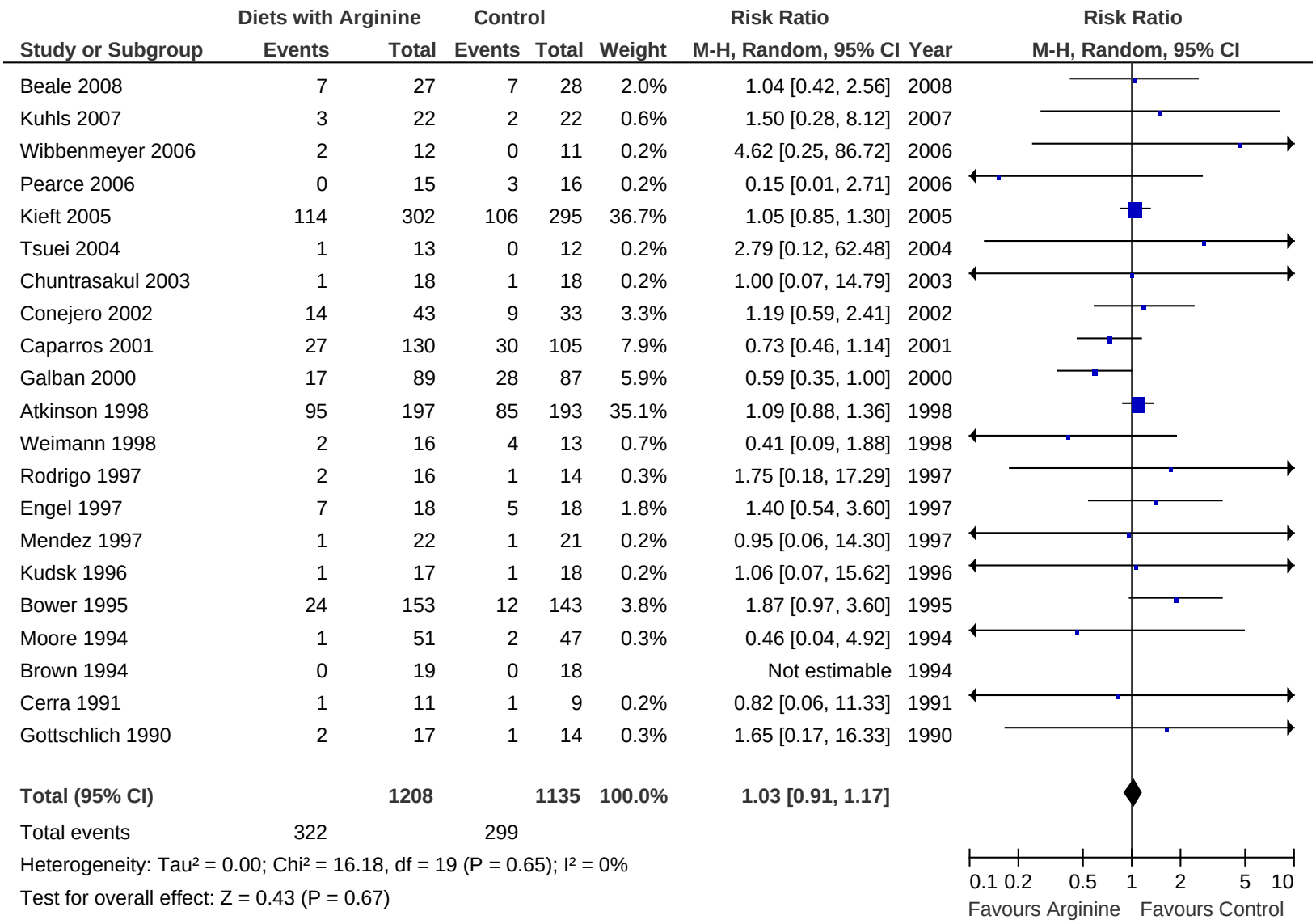
[8] The I^2 statistic for Hospital Length of Stay is 85%. Desired is < 50%

[9] Deaths are not handled uniformly in the reporting of the included studies. Uncertain if early death drove down the LOS in any study.

[10] Studies performed prior to 1996 favor the experimental formula, while studies performed since 2005 favor the control formula

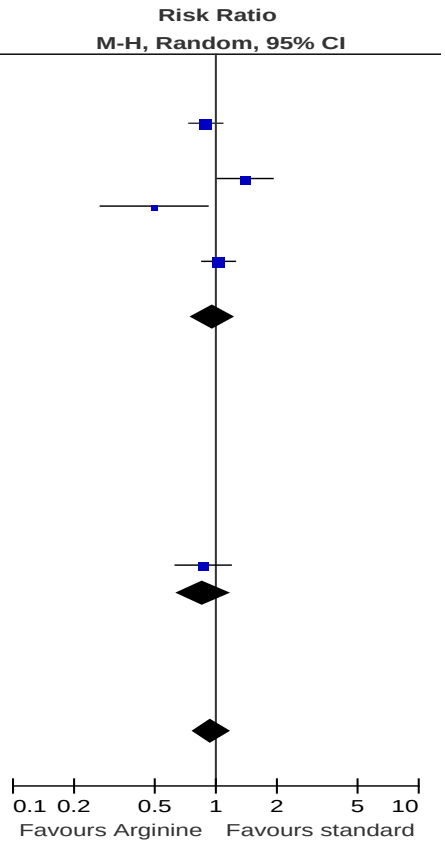
[11] The study was not powered to detect a difference in LOS variables.

Immune Modulating EN vs. Standard EN, Outcome: Mortality


Diets with Arginine
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Year
M-H, Random, 95% CI
Beale 2008 7 27 7 28 2.0% 1.04 [0.42, 2.56] 2008
Kuhls 2007 3 22 2 22 0.6% 1.50 [0.28, 8.12] 2007
Wibbenmeyer 2006 2 12 0 11 0.2% 4.62 [0.25, 86.72] 2006
Pearce 2006 0 15 3 16 0.2% 0.15 [0.01, 2.71] 2006
Kieft 2005 114 302 106 295 36.7% 1.05 [0.85, 1.30] 2005
Tsuei 2004 1 13 0 12 0.2% 2.79 [0.12, 62.48] 2004
Chuntrasakul 2003 1 18 1 18 0.2% 1.00 [0.07, 14.79] 2003
Conejero 2002 14 43 9 33 3.3% 1.19 [0.59, 2.41] 2002
Caparros 2001 27 130 30 105 7.9% 0.73 [0.46, 1.14] 2001
Galban 2000 17 89 28 87 5.9% 0.59 [0.35, 1.00] 2000
Atkinson 1998 95 197 85 193 35.1% 1.09 [0.88, 1.36] 1998
Weimann 1998 2 16 4 13 0.7% 0.41 [0.09, 1.88] 1998
Rodrigo 1997 2 16 1 14 0.3% 1.75 [0.18, 17.29] 1997
Engel 1997 7 18 5 18 1.8% 1.40 [0.54, 3.60] 1997
Mendez 1997 1 22 1 21 0.2% 0.95 [0.06, 14.30] 1997
Kudsk 1996 1 17 1 18 0.2% 1.06 [0.07, 15.62] 1996
Bower 1995 24 153 12 143 3.8% 1.87 [0.97, 3.60] 1995
Moore 1994 1 51 2 47 0.3% 0.46 [0.04, 4.92] 1994
Brown 1994 0 19 0 18 Not estimable 1994
Cerra 1991 1 11 1 9 0.2% 0.82 [0.06, 11.33] 1991
Gottschlich 1990 2 17 1 14 0.3% 1.65 [0.17, 16.33] 1990
Total (95% CI) 1208 1135 100.0% 1.03 [0.91, 1.17]
Total events 322 299
Heterogeneity: Tau² = 0.00; Chi² = 16.18, df = 19 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
0.1 0.2 0.5 1 2 5 10
Favours Arginine
Favours Control

Immune modulating formula versus Standard EN, Outcome: Infection, with sub analysis by study quality

Study or Subgroup	Diets wih Arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 High Quality Studies (8+)							
Brown 1994	3	19	10	18	0.0%	0.28 [0.09, 0.87]	1994
Bower 1995	86	153	90	143	26.3%	0.89 [0.74, 1.08]	1995
Kudsk 1996	5	16	11	17	0.0%	0.48 [0.22, 1.08]	1996
Caparros 2001	64	130	37	105	19.2%	1.40 [1.02, 1.91]	2001
Conejero 2002	11	43	17	33	8.8%	0.50 [0.27, 0.91]	2002
Tsuei 2004	8	13	6	11	0.0%	1.13 [0.57, 2.25]	2004
Kieft 2005	130	302	123	295	26.4%	1.03 [0.86, 1.24]	2005
Wibbenmeyer 2006	9	12	7	11	0.0%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		**628**		**576**	**80.8%**	**0.97 [0.75, 1.26]**	
Total events	291		267				
Heterogeneity: Tau² = 0.05; Chi² = 11.01, df = 3 (P = 0.01); I² = 73%							
Test for overall effect: Z = 0.23 (P = 0.82)							
1.2.2 Low Quality Studies (<8)							
Rodrigo 1997	5	16	3	14	0.0%	1.46 [0.42, 5.03]	1997
Mendez 1997	19	22	12	21	0.0%	1.51 [1.01, 2.27]	1997
Engel 1997	6	18	5	18	0.0%	1.20 [0.45, 3.23]	1997
Galban 2000	39	89	44	87	19.2%	0.87 [0.63, 1.19]	2000
Subtotal (95% CI)		**89**		**87**	**19.2%**	**0.87 [0.63, 1.19]**	
Total events	39		44				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
Total (95% CI)		**717**		**663**	**100.0%**	**0.95 [0.77, 1.18]**	
Total events	330		311				
Heterogeneity: Tau² = 0.03; Chi² = 11.59, df = 4 (P = 0.02); I² = 66%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%							

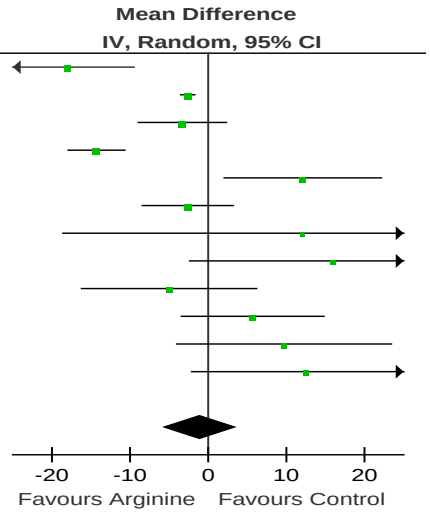


Immune modulating formula vs. Standard EN Outcome: LOS

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Cerra 1991	36.7	8.5	11	54.7	10.5	9	9.3%	-18.00 [-26.50, -9.50]	1991
Moore 1994	14.6	1.3	51	17.2	2.8	47	12.9%	-2.60 [-3.48, -1.72]	1994
Bower 1995	27.6	23	153	30.9	26	143	11.1%	-3.30 [-8.91, 2.31]	1995
Kudsk 1996	18.3	2.8	16	32.6	7	17	12.1%	-14.30 [-17.90, -10.70]	1996
Mendez 1997	34	21.2	22	21.9	11	21	8.3%	12.10 [2.07, 22.13]	1997
Atkinson 1998	20.6	26	197	23.2	32	193	10.9%	-2.60 [-8.39, 3.19]	1998
Weimann 1998	70.2	53	16	58.1	30	13	2.1%	12.10 [-18.57, 42.77]	1998
Chuntrasakul 2003	45	30	18	29	26	18	4.5%	16.00 [-2.34, 34.34]	2003
Tsuei 2004	22	9	13	27	17	11	7.7%	-5.00 [-16.17, 6.17]	2004
Pearce 2006	19.1	14.4	15	13.4	11.1	16	8.9%	5.70 [-3.39, 14.79]	2006
Kuhls 2007	40	23.45	22	30.3	22.98	22	6.3%	9.70 [-4.02, 23.42]	2007
Beale 2008	43.8	28	27	31.3	27.2	28	5.9%	12.50 [-2.10, 27.10]	2008
Total (95% CI)			**561**			**538**	**100.0%**	**-0.93 [-5.75, 3.89]**	

Heterogeneity: Tau² = 46.49; Chi² = 75.65, df = 11 (P < 0.00001); I² = 85%

Test for overall effect: Z = 0.38 (P = 0.71)

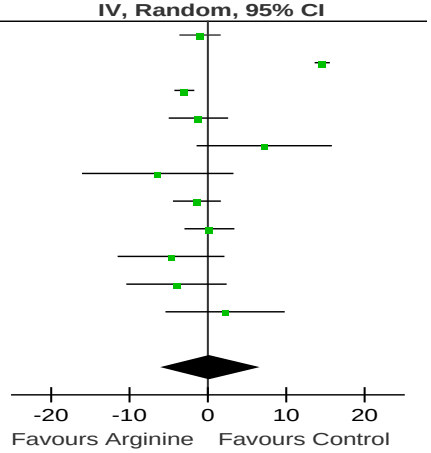


Immune Modulating Formula vs. Standard EN, Outcome: Ventilator Days

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Gottschlich 1990	9	4.5	17	10	2.5	14	9.6%	-1.00 [-3.51, 1.51]	1990
Moore 1994	19.9	0.9	51	5.3	3.1	57	9.7%	14.60 [13.76, 15.44]	1994
Kudsk 1996	2.4	1.3	16	5.4	2	17	9.7%	-3.00 [-4.14, -1.86]	1996
Engel 1997	14.8	5.6	18	16	5.6	18	9.4%	-1.20 [-4.86, 2.46]	1997
Mendez 1997	16.5	19.4	22	9.3	6	21	8.3%	7.20 [-1.30, 15.70]	1997
Weimann 1998	21.4	10.8	16	27.8	14.6	13	8.0%	-6.40 [-15.94, 3.14]	1998
Atkinson 1998	8	11.1	197	9.4	17.7	193	9.5%	-1.40 [-4.34, 1.54]	1998
Galban 2000	12.4	10.4	89	12.2	10.3	87	9.5%	0.20 [-2.86, 3.26]	2000
Chuntrasakul 2003	2.7	5.2	18	7.4	13.5	18	8.8%	-4.70 [-11.38, 1.98]	2003
Tsuei 2004	10	5	13	14	10	12	8.9%	-4.00 [-10.28, 2.28]	2004
Kuhls 2007	23.1	12.66	22	20.9	12.66	22	8.6%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			**479**			**472**	**100.0%**	**0.31 [-6.08, 6.70]**	

Heterogeneity: Tau² = 109.15; Chi² = 745.64, df = 10 (P < 0.00001); I² = 99%

Test for overall effect: Z = 0.09 (P = 0.92)



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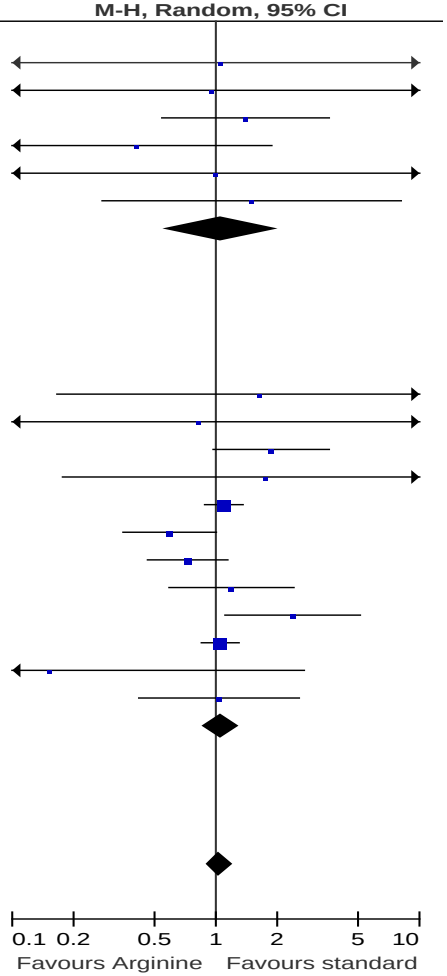
mmune Modulation formula vs. Standard Formula, Outcome: Mortality, with Trauma Sub-analysis

Study or Subgroup	Diets with Arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.8.1 Trauma patients							
Kudsk 1996	1	17	1	18	0.3%	1.06 [0.07, 15.62]	1996
Mendez 1997	1	22	1	21	0.3%	0.95 [0.06, 14.30]	1997
Engel 1997	7	18	5	18	2.7%	1.40 [0.54, 3.60]	1997
Weimann 1998	2	16	4	13	1.0%	0.41 [0.09, 1.88]	1998
Chuntrasakul 2003	1	18	1	18	0.3%	1.00 [0.07, 14.79]	2003
Kuhls 2007	3	22	2	22	0.9%	1.50 [0.28, 8.12]	2007
Subtotal (95% CI)		**113**		**110**	**5.6%**	**1.06 [0.55, 2.05]**	
Total events	15		14				
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 5 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.86)							
1.8.2 Non-trauma patients							
Gottschlich 1990	2	17	1	14	0.5%	1.65 [0.17, 16.33]	1990
Cerra 1991	1	11	1	9	0.4%	0.82 [0.06, 11.33]	1991
Bower 1995	24	153	12	143	5.3%	1.87 [0.97, 3.60]	1995
Rodrigo 1997	2	16	1	14	0.5%	1.75 [0.18, 17.29]	1997
Atkinson 1998	95	197	85	193	28.6%	1.09 [0.88, 1.36]	1998
Galban 2000	17	89	28	87	7.9%	0.59 [0.35, 1.00]	2000
Capparos 2001	27	130	30	105	10.2%	0.73 [0.46, 1.14]	2001
Conejero 2002	14	43	9	33	4.6%	1.19 [0.59, 2.41]	2002
Dent 2003	20	87	8	83	4.0%	2.39 [1.11, 5.11]	2003
Kieft 2005	114	302	106	295	29.3%	1.05 [0.85, 1.30]	2005
Pearce 2006	0	15	3	16	0.3%	0.15 [0.01, 2.71]	2006
Beale 2008	7	27	7	28	2.9%	1.04 [0.42, 2.56]	2008
Subtotal (95% CI)		**1087**		**1020**	**94.4%**	**1.05 [0.85, 1.30]**	
Total events	323		291				
Heterogeneity: Tau² = 0.04; Chi² = 16.88, df = 11 (P = 0.11); I² = 35%							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)		**1200**		**1130**	**100.0%**	**1.05 [0.89, 1.23]**	
Total events	338		305				
Heterogeneity: Tau² = 0.01; Chi² = 18.89, df = 17 (P = 0.33); I² = 10%							
Test for overall effect: Z = 0.57 (P = 0.57)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%							



Should fiber-containing vs. standard EN be used for diarrhea?

Question: Should Fiber containing EN versus Standard EN be used for diarrhea?

Hart 1988; Schultz 2000; Spapen 2001 & Chittawatanarat 2010

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Fiber containing EN versus Standard EN**		**Risk with Control**	**Risk difference with Fiber containing EN versus Standard EN** (95% CI)
Diarrhea (CRITICAL OUTCOME)											
171 (4 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness[3]	serious[4]	undetected	**LOW**[1,2,3,4] due to inconsistency, imprecision	39/73 (53.4%)	40/98 (40.8%)	**RR 0.75** (0.43 to 1.31)	**Study population**	
										534 per 1000	**134 fewer per 1000** (from 305 fewer to 166 more)
										Moderate	
										523 per 1000	**131 fewer per 1000** (from 298 fewer to 162 more)

[1] Major risk of bias is not including all randomized subjects in the denominator when doing analysis

[2] Jevity Plus or Nepro+pectin, Promote +pectin, formula with added guar gum, Osmolite HN + Fybogel, or Nutren fiber+ FOS and pectin and insoluble fibers were intervention formula. Standard formula included Nutren Optimum, Osmolite, Promote, Osmolite HN vs unspecified standard formula

[3] Definition of diarrhea not stated

[4] Low number of subjects in included studies

Question E4b: Peptide-based vs Standard EN

Question: Should Peptide-based EN versus Standard EN be used for Diarrhea

Bibliography: Brinson 1988; Meridith 1990; Mowatt-Larson 1992 & Heimburger 1997

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Peptide EN versus Standard EN**		**Risk with Control**	**Risk difference with Peptide EN versus Standard EN** (95% CI)
Diarrhea (CRITICAL OUTCOME)											
121 (4 studies)	serious[1]	serious[2]	no serious indirectness[3]	no serious imprecision	undetected	**LOW**[1,2,3] due to risk of bias, inconsistency	17/58 (29.3%)	17/63 (27%)	**RR 0.76** (0.25 to 2.33)	**293 per 1000**	**70 fewer per 1000** (from 220 fewer to 390 more)

[1] Blinding and intention to treat analysis are the major threats of bias in the 4 included studies

[2] Vital, Reablilan HN, and unspecified "small peptide" formula were the intervention formula. Control formula included Osmolite HN, Isocal and unspecified "whole protein" formula.

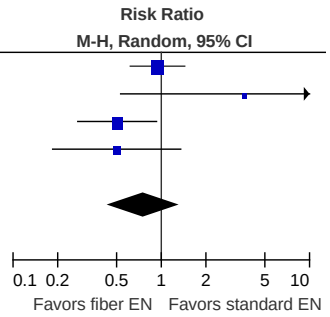
[3] Definition of diarrhea not stated

Fiber EN versus Standard EN, Outcome Diarrhea

Study or Subgroup	Fiber containing EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hart 1988	19	35	19	33	40.6%	0.94 [0.62, 1.44]	1988
Schultz 2000	11	33	1	11	7.2%	3.67 [0.53, 25.26]	2000
Spapen 2001	6	13	11	12	32.4%	0.50 [0.27, 0.93]	2001
Chittawatanarat 2010	4	17	8	17	19.8%	0.50 [0.18, 1.35]	2010
Total (95% CI)		**98**		**73**	**100.0%**	**0.75 [0.43, 1.31]**	
Total events	40		39				

Heterogeneity: Tau² = 0.15; Chi² = 6.21, df = 3 (P = 0.10); I² = 52%

Test for overall effect: Z = 1.01 (P = 0.31)

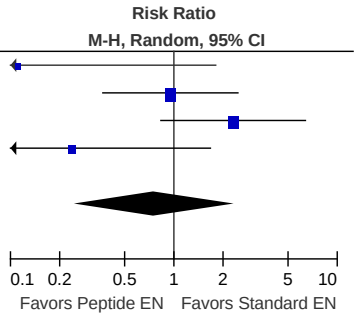


Peptide EN vs. Standard EN, Outcome Diarrhea

Study or Subgroup	Peptide EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Meredith 1990	0	9	4	9	12.0%	0.11 [0.01, 1.80]	1990
Mowatt-Larson 1992	6	21	6	20	34.9%	0.95 [0.37, 2.47]	1992
Heimburger 1997	10	26	4	24	33.7%	2.31 [0.83, 6.39]	1997
Brinson 1998	1	7	3	5	19.4%	0.24 [0.03, 1.67]	1998
Total (95% CI)		**63**		**58**	**100.0%**	**0.76 [0.25, 2.33]**	
Total events	17		17				

Heterogeneity: Tau² = 0.70; Chi² = 7.20, df = 3 (P = 0.07); I² = 58%

Test for overall effect: Z = 0.48 (P = 0.63)



Does the provision of antioxidants and trace minerals affect outcome in critically ill adult patients?

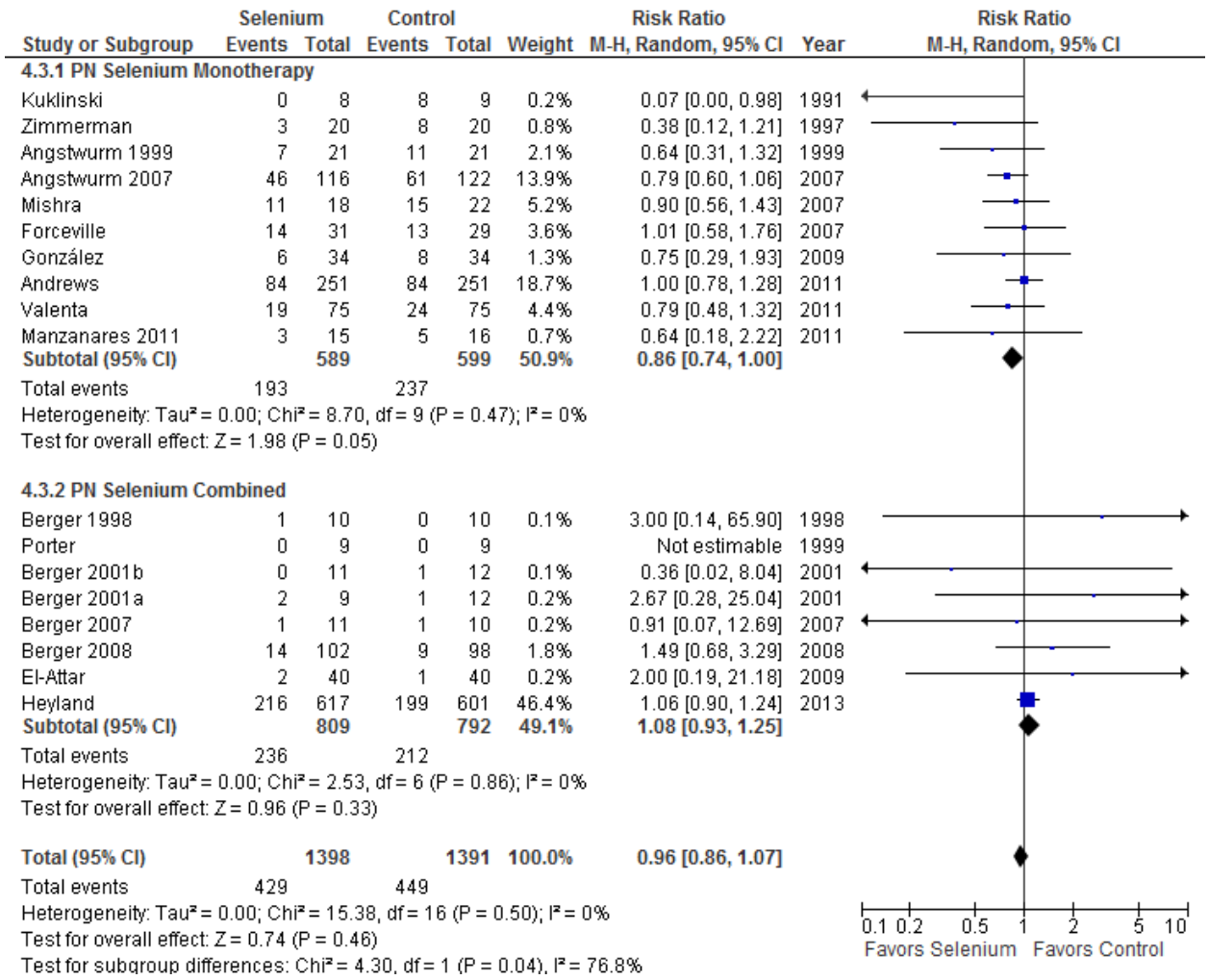
Question: Selenium											
Quality assessment							**Summary of Findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Antioxidants (Selenium; single+ combined)**		**Risk with Control**	**Risk difference with Antioxidants (Selenium; single+ combined)** (95% CI)
Mortality (Se alone)											
1341 (11)	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	undetected	**LOW**[1,2] due to inconsistency, imprecision	239/675 (35.4%)	203/666 (30.5%)	**RR 0.88** (0.74 to 1.04)	**Study population**	
										354 per 1000	**42 fewer per 1000** (from 92 fewer to 14 more)
Infections subgroup analyses: PN selenium monotherapy vs combined											
2321 (9 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[4]	undetected	**MODERATE**	378/1155 (32.7%)	339/1166 (29.1%)	**RR 0.88** (0.78 to 0.99)	**Study population**	
										327 per 1000	**39 fewer per 1000** (from 3 fewer to 72 fewer)
ICU LOS (Better indicated by lower values)											
1830 (10 studies)	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	undetected	**LOW**[1,2] due to inconsistency, imprecision	912	918	**-**		The mean icu los in the intervention groups was **0.47 higher** (0.7 lower to 1.64 higher)

Hospital LOS (Better indicated by lower values)										
1500 (6 studies)	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	undetected	**LOW**[1,2] due to inconsistency, imprecision	742	758	**-**	The mean hospital los in the intervention groups was **1.15 lower** (4.88 lower to 2.58 higher)
Ventilator Days (Better indicated by lower values)										
1412 (7 studies)	no serious risk of bias	serious[3]	no serious indirectness	serious[1]	undetected	**LOW**[1,3] due to inconsistency, imprecision	699	713	**-**	The mean ventilator days in the intervention groups was **1.76 lower** (4.9 lower to 1.38 higher)

[1] Combined estimate of effect size crosses the line of no effect.
[2] Wide confidence intervals
[3] Heterogenity among studies

[4]Infectious complications are heterogeneous among studies

Selenium vs Control, Outcome: Mortality

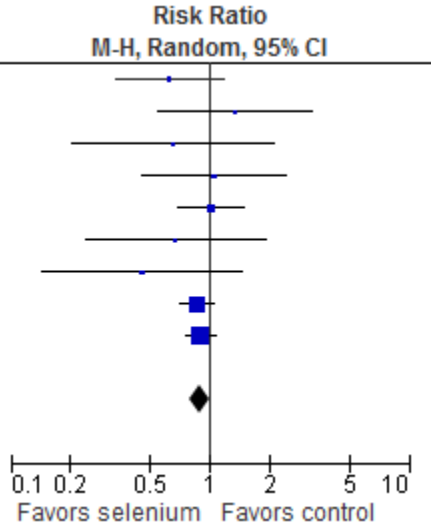


Selenium vs Control: Outcome Infectious Complications

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Porter	5	9	8	9	3.5%	0.63 [0.33, 1.17]	1999
Berger 2001a	5	9	5	12	1.7%	1.33 [0.55, 3.24]	2001
Berger 2001b	3	11	5	12	1.0%	0.65 [0.20, 2.12]	2001
Angstwurm 2007	10	116	10	122	2.0%	1.05 [0.45, 2.43]	2007
Berger 2008	36	102	34	98	9.6%	1.02 [0.70, 1.48]	2008
El-Attar	5	36	7	34	1.3%	0.67 [0.24, 1.92]	2009
Manzanares 2011	3	15	7	16	1.0%	0.46 [0.14, 1.45]	2011
Andrews	104	251	121	251	36.2%	0.86 [0.71, 1.04]	2011
Heyland	168	617	181	601	43.7%	0.90 [0.76, 1.08]	2013
Total (95% CI)		**1166**		**1155**	**100.0%**	**0.88 [0.78, 0.99]**	
Total events	339		378				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.60$, $df = 8$ ($P = 0.80$); $I^2 = 0\%$

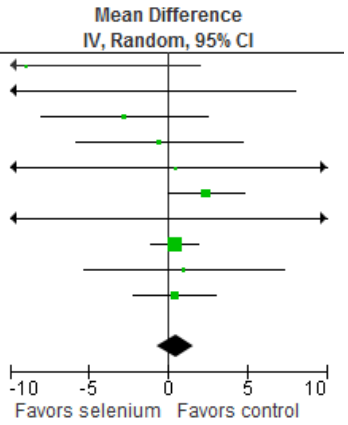
Test for overall effect: $Z = 2.08$ ($P = 0.04$)



Selenium vs Control: Outcome ICU LOS

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger 1998	30	12	10	39	13	10	1.1%	-9.00 [-19.97, 1.97]	1998
Porter	22	25.2	9	35.8	21.9	9	0.3%	-13.80 [-35.61, 8.01]	1999
Berger 2001b	5.8	4.4	11	8.6	8.1	12	4.8%	-2.80 [-8.07, 2.47]	2001
Berger 2001a	8	4	9	8.6	8.1	12	4.8%	-0.60 [-5.88, 4.68]	2001
Mishra	21.3	16.2	18	20.8	21.8	22	1.0%	0.50 [-11.29, 12.29]	2007
Angstwurm 2007	15.1	10	116	12.7	9	122	20.9%	2.40 [-0.02, 4.82]	2007
Berger 2007	35	27	11	47	37	10	0.2%	-12.00 [-39.94, 15.94]	2007
Berger 2008	5.8	5.4	102	5.4	5.7	98	44.9%	0.40 [-1.14, 1.94]	2008
Manzanares 2011	14	11	15	13	6	16	3.4%	1.00 [-5.30, 7.30]	2011
Heyland	14.2	22.7	617	13.8	23.1	601	18.7%	0.40 [-2.17, 2.97]	2013
Total (95% CI)			**918**			**912**	**100.0%**	**0.47 [-0.70, 1.64]**	

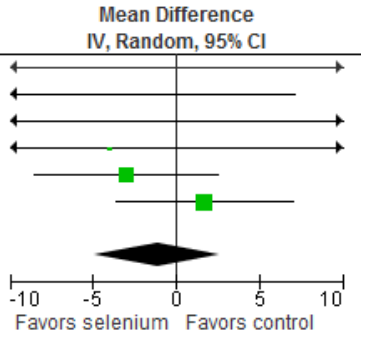
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 9.39$, df = 9 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 0.79 (P = 0.43)



Selenium vs Control: Outcome Hospital LOS

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berger 1998	54	27	10	66	31	10	2.1%	-12.00 [-37.48, 13.48]
Porter	31.3	23.4	9	49	30	9	2.3%	-17.70 [-42.56, 7.16]
Berger 2001a	82	78	9	64	39	12	0.5%	18.00 [-37.53, 73.53]
Berger 2001b	60	48	11	64	39	12	1.1%	-4.00 [-39.94, 31.94]
Berger 2008	23	20	102	26	20	98	45.3%	-3.00 [-8.54, 2.54]
Heyland	31.2	50.2	617	29.5	44.8	601	48.8%	1.70 [-3.64, 7.04]
Total (95% CI)			**758**			**742**	**100.0%**	**-1.15 [-4.88, 2.58]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.40$, df = 5 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.60 (P = 0.55)

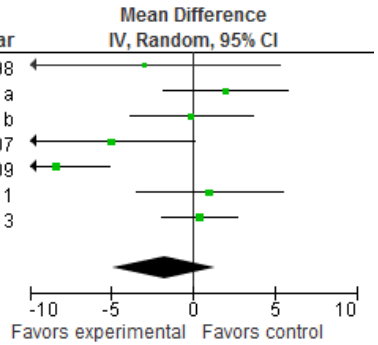


Selenium vs Control, Outcome Ventilator Days

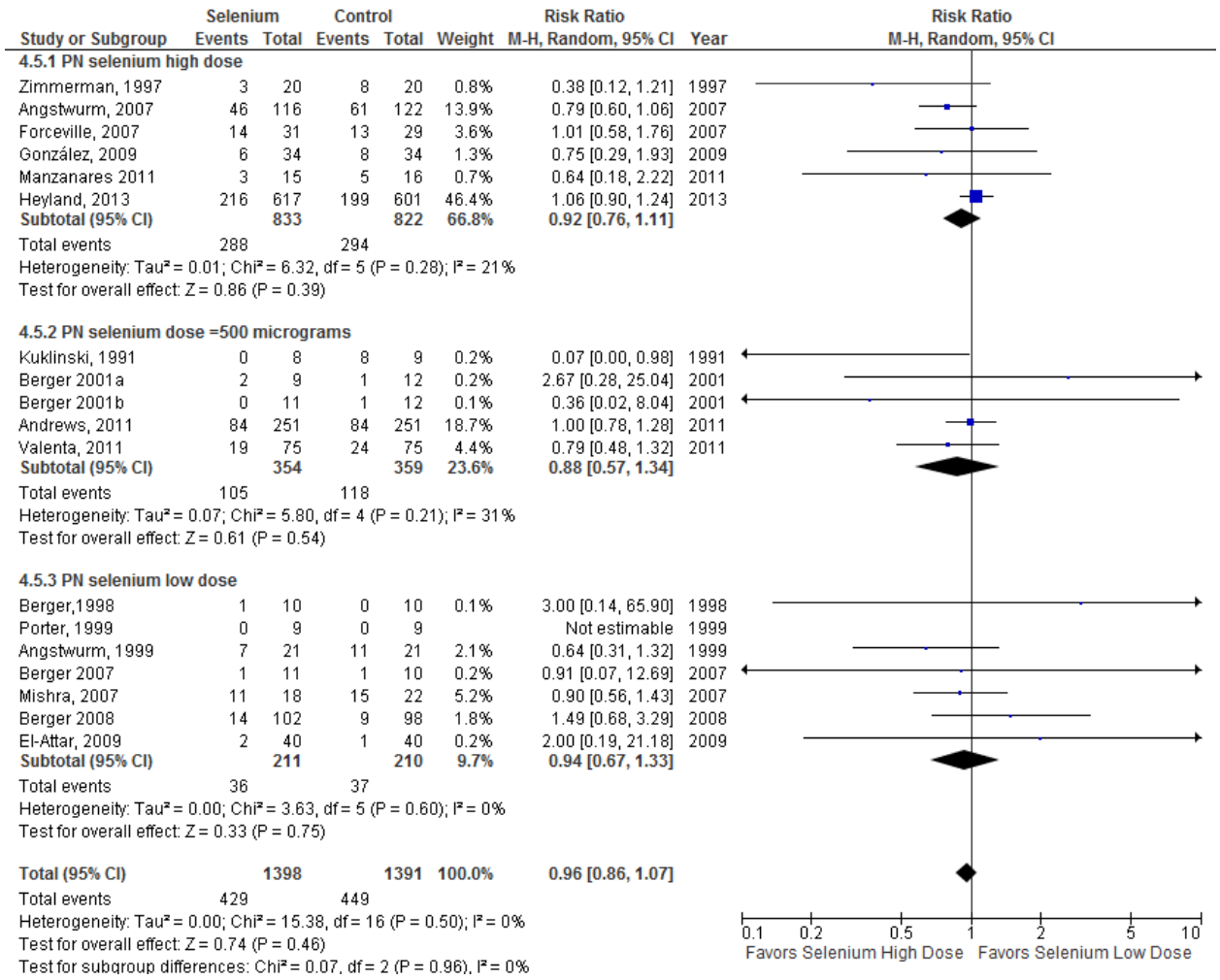
Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger '98	9	10	10	12	9	10	8.3%	-3.00 [-11.34, 5.34]	1998
Berger '01a	6.2	3.5	9	4.2	5.2	11	15.3%	2.00 [-1.83, 5.83]	2001a
Berger '01b	4.1	3.6	11	4.2	5.2	11	15.4%	-0.10 [-3.84, 3.64]	2001b
Berger 2007	7.6	6	11	12.6	6	10	12.9%	-5.00 [-10.14, 0.14]	2007
El-Attar	9.4	7.3	40	17.8	7.6	40	16.3%	-8.40 [-11.67, -5.13]	2009
Manzanares 2011	10	8	15	9	4	16	14.0%	1.00 [-3.50, 5.50]	2011
Heyland	10.9	21.4	617	10.5	19.7	601	17.8%	0.40 [-1.91, 2.71]	2013
Total (95% CI)			**713**			**699**	**100.0%**	**-1.76 [-4.90, 1.38]**	

Heterogeneity: Tau² = 13.00; Chi² = 26.59, df = 6 (P = 0.0002); I² = 77%

Test for overall effect: Z = 1.10 (P = 0.27)



Selenium Dose, Outcome: Mortality



Does glutamine added to EN improve outcomes vs. STD EN

Question: EN with added glutamine vs. STD EN made isonitrogenous for critically ill adult

Houdijk 1998; Jones, 1999; Hall 2003; Garrell 2003; McQuiggan 2008

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With STD EN made isonitrogenous	With EN with added glutamine		Risk with STD EN made isonitrogenous	Risk difference with EN with added glutamine (95% CI)
Mortality (CRITICAL OUTCOME)											
558 subjects (5 studies)	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	serious[3,4]	undetected	**MODERATE**[1,2,3,4] due to imprecision	56/281 (19.9%)	43/277 (15.5%)	**RR 0.8** (0.45 to 1.43)	**199 per 1000**	**40 fewer per 1000** (from 110 fewer to 86 more)
Infections (CRITICAL OUTCOME)											
476 subjects (3 studies)	no serious risk of bias[5]	no serious inconsistency[6]	no serious indirectness	serious[4]	undetected	**LOW**[4,5,6] due to inconsistency, imprecision	79/243 (32.5%)	65/233 (27.9%)	**RR 0.85** (0.66 to 1.09)	**325 per 1000**	**49 fewer per 1000** (from 111 fewer to 29 more)
Hospital stay in days (CRITICAL OUTCOME; Better indicated by lower values)											
125 subjects (2 studies)	no serious risk of	no serious inconsistency	no serious indirectness	serious[4]	undetected	**MODERATE**[4,5] due to imprecision	63	62	-		The mean hospital stay in days in the

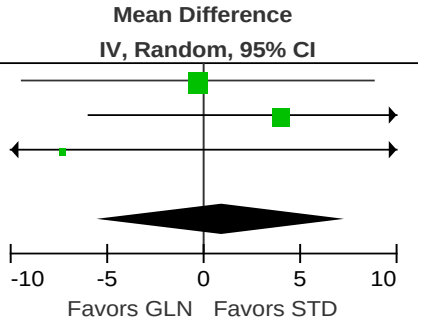
	bias[5]								intervention groups was **1.66 higher** (5.06 lower to 8.39 higher)

[1] Major bias is two studies published prior to 2000 did not use intention to treat analysis. Otherwise, methods were good.
[2] Heterogeneity was desirable, the I2 statistic + 37%. Less than 50% is desirable.
[3] As expected, smaller studies have wider confidence intervals.
[4] The estimate of effect crosses the line of no effect.
[5] A major bias is Houdijk 1998 did not use intention to treat analysis.
[6] One study used positive blood cultures as the indicator of infection versus severe sepsis as defined by ACCP and SCCM

EN Glutamine vs Standard, Outcome: Hospital LOS

	En with GLN			STD with PRO				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Houdijk 1998	32.7	17.1	41	33	23.8	39	49.9%	-0.30 [-9.42, 8.82]	1998
Garrell 2003	33	17	21	29	17	24	41.9%	4.00 [-5.96, 13.96]	2003
McQuiggan 2008	32	13.6	10	39.3	33.6	10	8.2%	-7.30 [-29.77, 15.17]	2008
Total (95% CI)			**72**			**73**	**100.0%**	**0.93 [-5.52, 7.37]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)

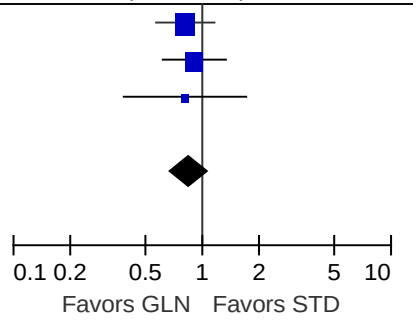


EN Glutamine vs Standard, Outcome: Infections

Study or Subgroup	En with GLN Events	Total	STD with PRO Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk 1998	20	35	26	37	48.1%	0.81 [0.57, 1.16]	1998
Hall 2003	38	179	43	184	41.0%	0.91 [0.62, 1.33]	2003
Garrell 2003	7	19	10	22	10.9%	0.81 [0.38, 1.71]	2003
Total (95% CI)		**233**		**243**	**100.0%**	**0.85 [0.66, 1.09]**	
Total events	65		79				

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%

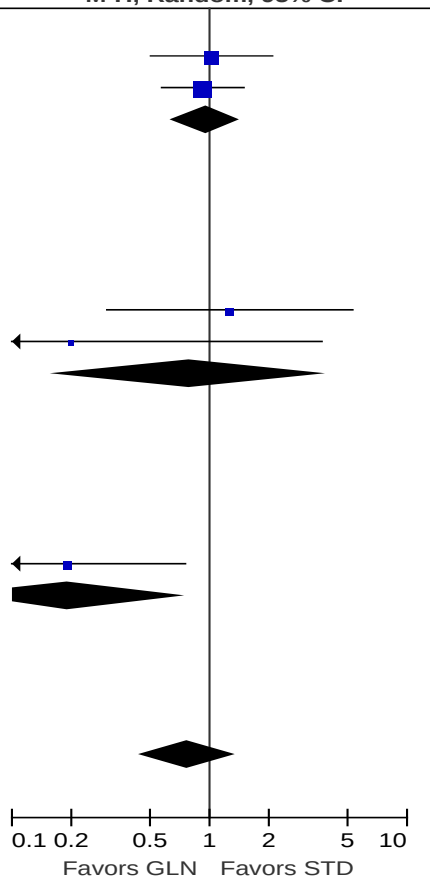
Test for overall effect: Z = 1.29 (P = 0.20)



[1]Garrell 2003 defined infection as positive blood culture.

EN Glutamine vs Standard, Outcome: Mortality

Study or Subgroup	En with GLN Events	Total	STD with PRO Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Mixed ICUNew Subgroup							
Jones 1999	10	26	9	24	30.3%	1.03 [0.50, 2.08]	1999
Hall 2003	27	179	30	184	41.1%	0.93 [0.57, 1.49]	2003
Subtotal (95% CI)		**205**		**208**	**71.3%**	**0.96 [0.64, 1.42]**	
Total events	37		39				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%							
Test for overall effect: Z = 0.23 (P = 0.82)							
1.1.2 Trauma							
Houdijk 1998	4	41	3	39	12.2%	1.27 [0.30, 5.31]	1998
McQuiggan 2008	0	10	2	10	3.5%	0.20 [0.01, 3.70]	2008
Subtotal (95% CI)		**51**		**49**	**15.7%**	**0.79 [0.16, 3.92]**	
Total events	4		5				
Heterogeneity: Tau² = 0.37; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%							
Test for overall effect: Z = 0.29 (P = 0.77)							
1.1.3 Burns							
Garrell 2003	2	21	12	24	13.0%	0.19 [0.05, 0.76]	2003
Subtotal (95% CI)		**21**		**24**	**13.0%**	**0.19 [0.05, 0.76]**	
Total events	2		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.36 (P = 0.02)							
Total (95% CI)		**277**		**281**	**100.0%**	**0.77 [0.44, 1.34]**	
Total events	43		56				
Heterogeneity: Tau² = 0.14; Chi² = 6.36, df = 4 (P = 0.17); I² = 37%							
Test for overall effect: Z = 0.93 (P = 0.35)							
Test for subgroup differences: Chi² = 4.87, df = 2 (P = 0.09), I² = 58.9%							



When should Parenteral Nutrition be initiated in the adult critically ill patient?

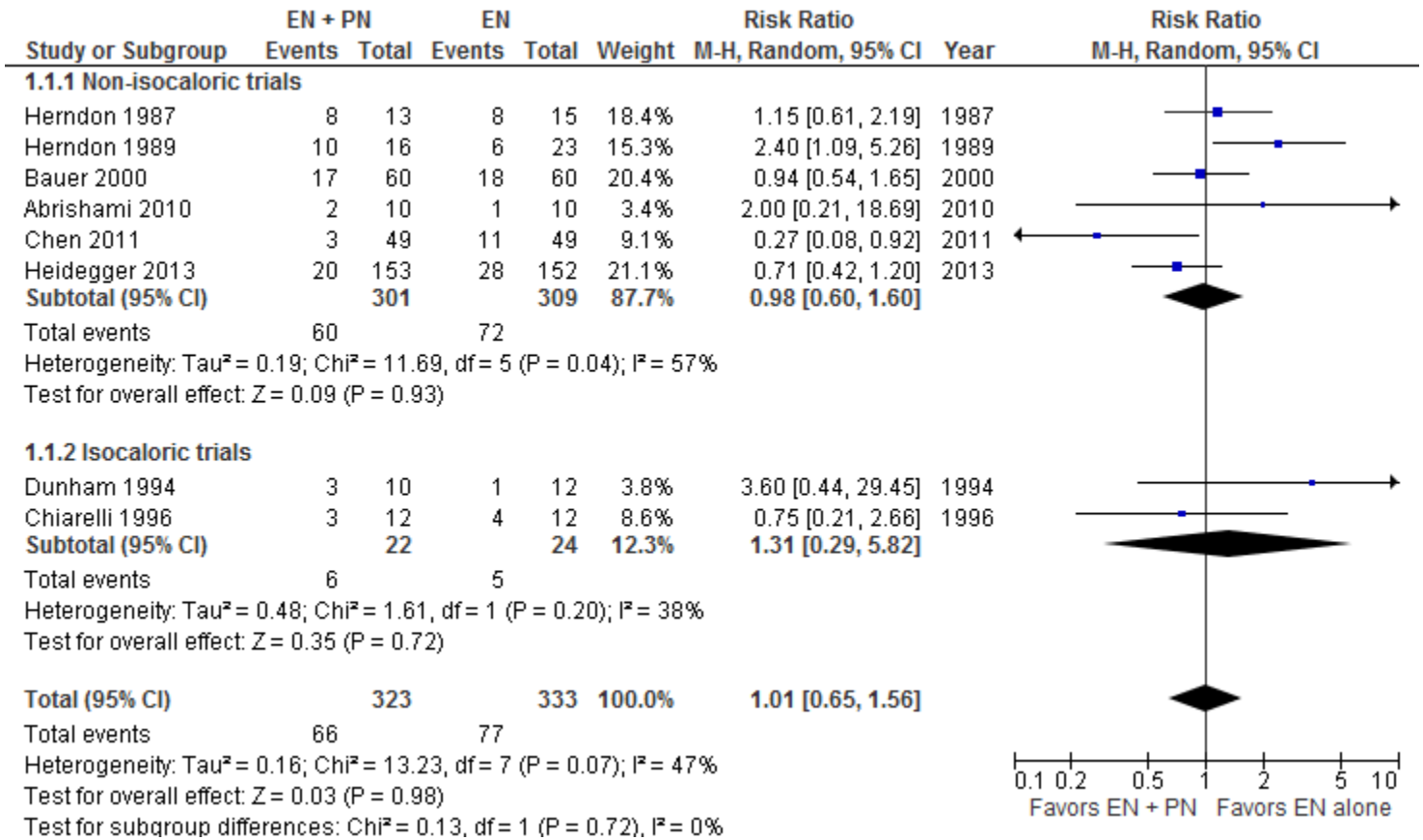
Question: Combination PN and EN vs EN alone for Critical Illness

Bibliography: Abrishami 2010; Bauer 2000; Chen 2011; Chiarelli 1996; Dunham 1994; Heidegger 2013; Herndon 1987; Herndon 1989

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With EN alone	With Combination PN and EN		Risk with EN alone	Risk difference with Combination PN and EN (95% CI)
Mortality											
656 (8 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	undetected	**LOW**[1,2,3] due to inconsistency, imprecision	77/333 (23.1%)	66/323 (20.4%)	**RR 1.01** (0.65 to 1.56)	**Study population**	
										231 per 1000	**2 more per 1000** (from 81 fewer to 129 more)
Mortality - Non-isocaloric trials											
610 (6 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	undetected	**LOW**[1,2,3] due to inconsistency, imprecision	72/309 (23.3%)	60/301 (19.9%)	**RR 0.98** (0.6 to 1.6)	**Study population**	
										233 per 1000	**5 fewer per 1000** (from 93 fewer to 140 more)
Mortality - Isocaloric trials											
46 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]			5/24 (20.8%)	6/22 (27.3%)	**RR 1.31** (0.29 to 5.82)	**Study population**	
										208 per 1000	**65 more per 1000** (from 148 fewer to 1000 more)

Infectious Complications											
547 (4 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	**MODERATE**[3] due to imprecision	132/273 (48.4%)	128/274 (46.7%)	**RR 0.96** (0.81 to 1.13)	**Study population**	
										484 per 1000	**19 fewer per 1000** (from 92 fewer to 63 more)
Hospital length of stay (Better indicated by lower values)											
547 (4 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1] due to risk of bias	273	274	**-**		The mean hospital length of stay in the intervention groups was **4.59 lower** (7.27 to 1.91 lower)
ICU length of stay (Better indicated by lower values)											
523 (3 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	**LOW**[1,3] due to risk of bias, imprecision	261	262	**-**		The mean icu length of stay in the intervention groups was **1.39 lower** (3.13 lower to 0.36 higher)
Ventilator days (Better indicated by lower values)											
547 (4 studies)	serious[1]	serious[2]	no serious indirectness	serious[3]	undetected	**VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	273	274	**-**		The mean ventilator days in the intervention groups was **0.74 lower** (2.29 lower to 0.82 higher)

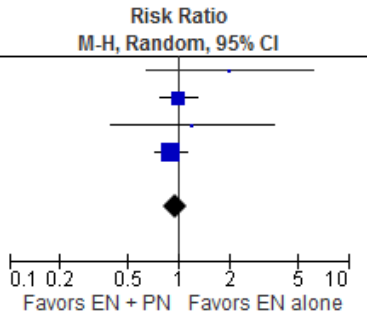
Supplemental PN vs EN Alone, Outcome: Mortality



Supplemental PN vs EN Alone, Outcome: Infectious Complications

Study or Subgroup	EN + PN Events	EN + PN Total	EN Events	EN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chiarelli 1996	6	12	3	12	2.0%	2.00 [0.65, 6.20]	1996
Bauer 2000	39	60	39	60	37.7%	1.00 [0.77, 1.30]	2000
Chen 2011	6	49	5	49	2.1%	1.20 [0.39, 3.67]	2011
Heidegger 2013	77	153	85	152	58.2%	0.90 [0.73, 1.11]	2013
Total (95% CI)		**274**		**273**	**100.0%**	**0.96 [0.81, 1.13]**	
Total events	128		132				

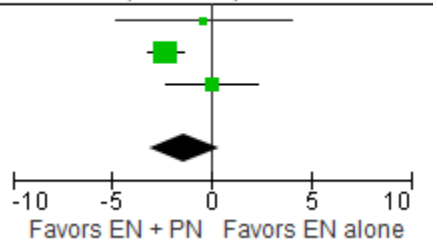
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)



Supplemental PN vs EN Alone, Outcome: ICU Length of Stay

Study or Subgroup	EN + PN Mean	EN + PN SD	EN + PN Total	EN Mean	EN SD	EN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Bauer 2000	16.9	11.8	60	17.3	12.8	60	12.7%	-0.40 [-4.81, 4.01]	2000
Chen 2011	6.75	1.75	49	9.09	2.75	49	57.1%	-2.34 [-3.25, -1.43]	2011
Heidegger 2013	13	10	153	13	11	152	30.2%	0.00 [-2.36, 2.36]	2013
Total (95% CI)			**262**			**261**	**100.0%**	**-1.39 [-3.13, 0.36]**	

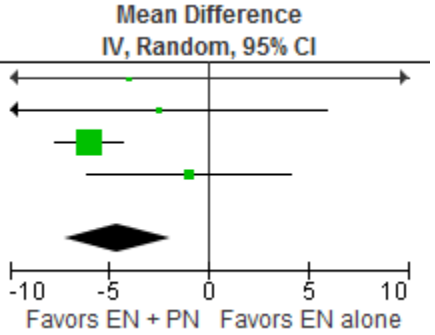
Heterogeneity: Tau² = 1.17; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.56 (P = 0.12)



Supplemental PN vs EN Alone, Outcome: Hospital Length of Stay

Study or Subgroup	EN + PN Mean	EN + PN SD	EN + PN Total	EN Mean	EN SD	EN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Chiarelli 1996	37	13	12	41	23	12	3.1%	-4.00 [-18.95, 10.95]	1996
Bauer 2000	31.2	18.5	60	33.7	27.7	60	9.1%	-2.50 [-10.93, 5.93]	2000
Chen 2011	17.3	2.47	49	23.32	5.6	49	66.9%	-6.02 [-7.73, -4.31]	2011
Heidegger 2013	31	23	153	32	23	152	20.9%	-1.00 [-6.16, 4.16]	2013
Total (95% CI)			**274**			**273**	**100.0%**	**-4.59 [-7.27, -1.91]**	

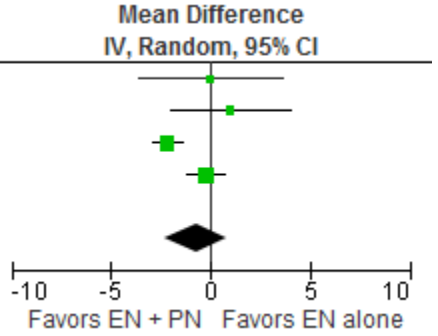
Heterogeneity: Tau² = 2.03; Chi² = 3.78, df = 3 (P = 0.29); I² = 21%
Test for overall effect: Z = 3.35 (P = 0.0008)



Supplemental PN vs EN Alone, Outcome: Ventilator Days

Study or Subgroup	EN + PN Mean	EN + PN SD	EN + PN Total	EN Mean	EN SD	EN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Chiarelli 1996	19	6	12	19	2	12	12.8%	0.00 [-3.58, 3.58]	1996
Bauer 2000	11	9	60	10	8	60	15.8%	1.00 [-2.05, 4.05]	2000
Chen 2011	5.76	1.56	49	7.95	2.11	49	36.8%	-2.19 [-2.92, -1.46]	2011
Heidegger 2013	2.5	4.625	153	2.75	4.21	152	34.5%	-0.25 [-1.24, 0.74]	2013
Total (95% CI)			**274**			**273**	**100.0%**	**-0.74 [-2.29, 0.82]**	

Heterogeneity: Tau² = 1.57; Chi² = 12.56, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.93 (P = 0.35)



Should low dose of PN vs Standard be used initially?

Question H2: Low dose PN (14-28.5 kcal/kg/d) vs., Standard (18-37 kcal/kg/d) for

Bibliography:

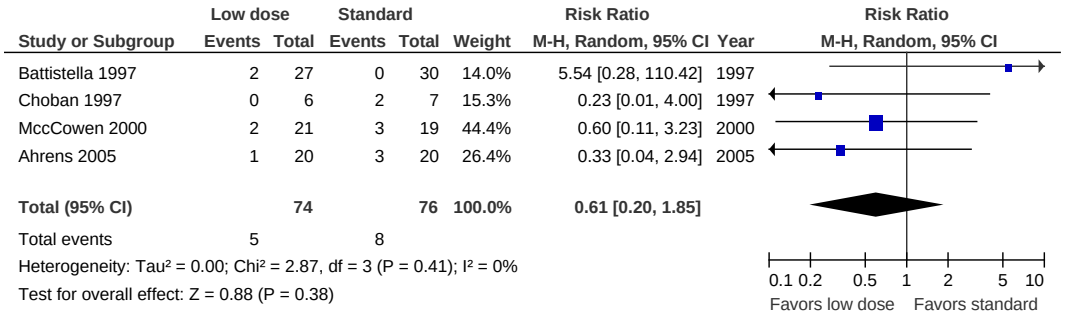
Battistella 1997, Choban 1997, McCowen 2000 & Ahrens 2005

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard (18-37 kcal/kg/d)	**With Low dose PN (14-28.5 kcal/kg/d)**		**Risk with Standard (18-37 kcal/kg/d)**	**Risk difference with Low dose PN (14-28.5 kcal/kg/d)** (95% CI)
Mortality (CRITICAL OUTCOME)											
150 (4 studies) 1-3 months	serious[1,2]	serious[3]	no serious indirectness	serious	undetected	**VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	8/76 (10.5%)	5/74 (6.8%)	**RR 0.61** (0.2 to 1.85)	**105 per 1000**	**41 fewer per 1000** (from 84 fewer to 89 more)
Infections (CRITICAL OUTCOME)											
137 (3 studies) 1-3 months	serious[1,2]	serious[3]	no serious indirectness	serious	undetected	**VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	25/69 (36.2%)	16/68 (23.5%)	**RR 0.68** (0.3 to 1.57)	**362 per 1000**	**116 fewer per 1000** (from 254 fewer to 207 more)
LOS days (CRITICAL OUTCOME; Better indicated by lower values)											
110 (3	serious[1,2]	serious[3]	no serious	serious	undetected	**VERY LOW**[1,2,3] due to risk of bias,	56	54	-		The mean los days in the intervention groups was

studies) 1-3 months			indirectness			inconsistency, imprecision				**3.94 lower** (14.51 lower to 6.64 higher)
Patients with hyperglycemia										
40 (1 study) 1-3 months	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1,2] due to risk of bias	14/20 (70%) 5/20 (25%)	**RR 0.36** (0.16 to 0.8)	**700 per 1000**	**448 fewer per 1000** (from 140 fewer to 588 fewer)

[1] Subjects and or outcome assessors were not blinded in all studies.
[2] Not all subjects randomized are included in the analysis.
[3] Wide range across studies for the following definitions (a) low dose and (b) standard PN.
[4] Sample sizes are very small and there are very wide confidence intervals that cross the line of no effect for all studies.

PN Energy Dose, Outcome: Mortality

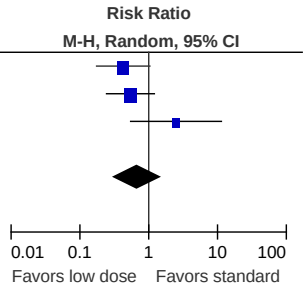


PN Energy Dose, Outcome: Infectious Complication

Study or Subgroup	Low dose Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Battistella 1997	5	27	13	30	37.9%	0.43 [0.18, 1.04]	1997
MccCowen 2000	6	21	10	19	41.3%	0.54 [0.24, 1.21]	2000
Ahrens 2005	5	20	2	20	20.8%	2.50 [0.55, 11.41]	2005
Total (95% CI)		**68**		**69**	**100.0%**	**0.68 [0.30, 1.57]**	
Total events	16		25				

Heterogeneity: Tau² = 0.27; Chi² = 4.05, df = 2 (P = 0.13); I² = 51%

Test for overall effect: Z = 0.90 (P = 0.37)

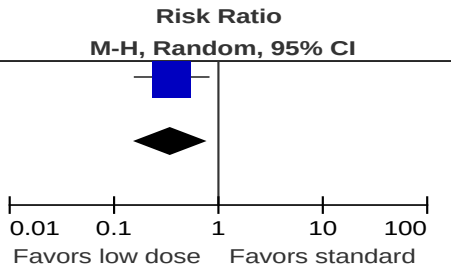


PN Energy Dose, Outcome: Subjects with hyperglycemia

Study or Subgroup	Low dose Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ahrens 2005	5	20	14	20	100.0%	0.36 [0.16, 0.80]	2005
Total (95% CI)		**20**		**20**	**100.0%**	**0.36 [0.16, 0.80]**	
Total events	5		14				

Heterogeneity: Not applicable

Test for overall effect: Z = 2.49 (P = 0.01)



Should Lipid be used with PN?

Question: Parenteral Nutrition With and Without Lipids

Bibliography: Bsttoste;;a 1997 & McCowan 2000

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Without lipids in PN in Critically Ill Patients	**With With lipids**		**Risk with Without lipids in PN in Critically Ill Patients**	**Risk difference with With lipids** (95% CI)
Mortality (CRITICAL OUTCOME)											
97 (2 studies)	serious[1]	serious[2]	no serious indirectness	serious[3]	undetected	**VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	4/48 (8.3%)	3/49 (6.1%)	**RR 0.77** (0.09 to 6.37)	**83 per 1000**	**19 fewer per 1000** (from 76 fewer to 447 more)
Infections (CRITICAL OUTCOME)											
97 (2 studies)	serious[1]	serious[4]	no serious indirectness	serious[3]	undetected	**VERY LOW**[1,3,4] due to risk of bias, inconsistency, imprecision	11/48 (22.9%)	23/49 (46.9%)	**RR 2.05** (1.13 to 3.72)	**Study population**	
										229 per 1000	**241 more per 1000** (from 30 more to 623 more)
										Moderate	
										235 per 1000	**247 more per 1000** (from 31 more to 639 more)
Hospital Length of Stay (CRITICAL OUTCOME; Better indicated by lower values)											

97 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	very serious[5,6]	undetected	**VERY LOW**[1,5,6] due to risk of bias, imprecision	48	49	**-**		The mean hospital length of stay in the intervention groups was **3.95 higher** (2.89 lower to 10.79 higher)

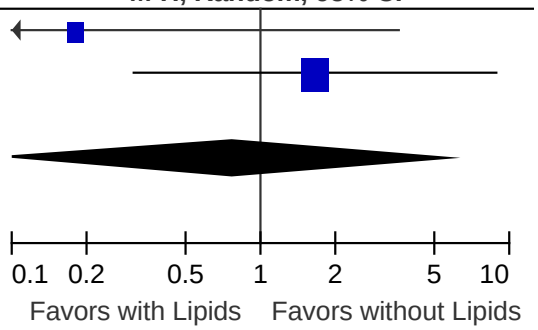
[1] The included studies did not blind interventions, nor did they use all subjects randomized in the data analysis.
[2] The RR of one study favors PN without lipids (Battistella 1997) while the the other favors McCowan 2000.
[3] Small number of subjects with small number of events.
[4] Infection type is not defined. Beattistella (1997) reported pneumonia and line sepsis. Line sepsis is included in this analysis. McCowen (2000) did not denote specific infections; only reported "infections".
[5] The studies were not powered to detect a difference on this variable.
[6] Uncertain if early deaths decreased LOS in any group. Cannot tell if reported effect is from the intervention or if early death affected the outcome.

PN Lipids, Outcome: Mortality

	With Lipids		Without Lipids			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Battistella 1997	0	30	2	27	34.4%	0.18 [0.01, 3.60]	1997
McCowan 2000	3	19	2	21	65.6%	1.66 [0.31, 8.88]	2000
Total (95% CI)		**49**		**48**	**100.0%**	**0.77 [0.09, 6.37]**	
Total events	3		4				

Heterogeneity: Tau² = 1.03; Chi² = 1.67, df = 1 (P = 0.20); I² = 40%

Test for overall effect: Z = 0.24 (P = 0.81)

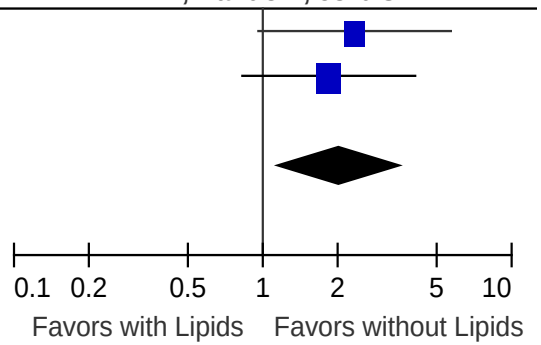


PN Lipids, Outcome: Infectious Complication

Study or Subgroup	With Lipids Events	Total	Without Lipids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Battistella 1997	13	30	5	27	44.6%	2.34 [0.96, 5.70]	1997
McCowan 2000	10	19	6	21	55.4%	1.84 [0.83, 4.10]	2000
Total (95% CI)		**49**		**48**	**100.0%**	**2.05 [1.13, 3.72]**	
Total events	23		11				

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%

Test for overall effect: Z = 2.36 (P = 0.02)

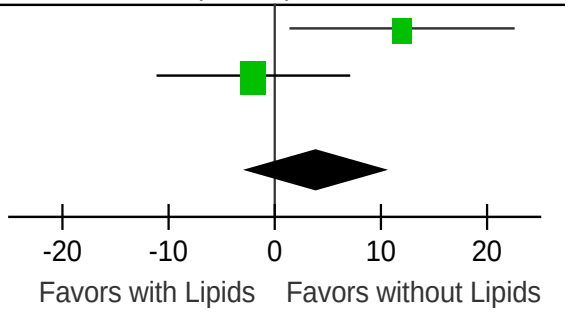


PN Lipids, Outcome: Hospital Length of Stay

Study or Subgroup	With Lipids Mean	SD	Total	Without Lipids Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Battistella 1997	39	24	30	27	16	27	42.5%	12.00 [1.50, 22.50]
McCowan 2000	17	15	19	19	14	21	57.5%	-2.00 [-11.02, 7.02]
Total (95% CI)			**49**			**48**	**100.0%**	**3.95 [-2.89, 10.79]**

Heterogeneity: Chi² = 3.93, df = 1 (P = 0.05); I² = 75%

Test for overall effect: Z = 1.13 (P = 0.26)



What is the appropriate target BG range in the ICU?

Question: Using insulin to maintain blood sugar in a tight range vs. conventional blood sugar management

Bibliography: Van den Berghe 2001; Grey 2004; Henderson 2005; Bland 2005; Mitchell 2006; Wang 2006; McMullin 2007; Farah 2007; Devos 2007; Mackenzie 2008; Iapichino 2008; De La Rosa 2008; Brunkhorst 2008; Arabi 2008; Finfer 2009; Savioli 2009; Annane 2010; Arabi 2011; Bilotta 2009; Finfer 2009 He 2007; He 2008; Oksanen 2007 Van den Berghe 2006 Yu 2005 Zhang 2008

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With conventional blood sugar management	**With Using insulin to maintain blood sugar in a tight range**		**Risk with conventional blood sugar management**	**Risk difference with Using insulin to maintain blood sugar in a tight range** (95% CI)
Mortality (overall) (CRITICAL OUTCOME)											
13861 (25 studies)	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1,2] due to risk of bias	1233/6907 (17.9%)	1165/6954 (16.8%)	**RR 0.91** (0.82 to 1.02)	**179 per 1000**	**16 fewer per 1000** (from 32 fewer to 4 more)
Infections (CRITICAL OUTCOME)											
2745 (6 studies)	no serious risk of bias[3]	serious[4]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[3,4] due to inconsistency	294/1374 (21.4%)	268/1371 (19.5%)	**RR 0.89** (0.73 to 1.09)	**214 per 1000**	**24 fewer per 1000** (from 58 fewer to 19 more)

LOS ICU days (CRITICAL OUTCOME; Better indicated by lower values)											
3777 (7 studies)	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[2] due to risk of bias	1898	1879	-	The mean los ICU days in the control groups was **17**	The mean los ICUdays in the intervention groups was **1.78 lower** (2.47 to 1.09 lower)
Ventilator days (CRITICAL OUTCOME; range of scores: 5-12.1; Better indicated by lower values)											
9649 (6 studies)	serious[5]	serious[4,5]	no serious indirectness	no serious imprecision	undetected	**LOW**[4,5] due to risk of bias, inconsistency	4835	4814	-	The mean ventilator days in the control groups was **8.7 days**	The mean ventilator days in the intervention groups was **1.41 lower** (2.58 to 0.23 lower)
Hypoglycemia (CRITICAL OUTCOME)											
11606 (18 studies)	serious[1,2]	serious[6]	no serious indirectness	serious[7]	undetected	**VERY LOW**[1,2,6,7] due to risk of bias, inconsistency, imprecision	305/5820 (5.2%)	866/5786 (15%)	**RR 3.19** (1.81 to 5.6)	**52 per 1000**	**115 more per 1000** (from 42 more to 241 more)

[1] In only 2/25 studies were personnel blinded. It is a difficult study to blind.

[2] In approximately one third of the studies, all subjects randomized were not included in the analysis (per protocol analysis) Intention to treat analysis is the stronger method of analysis.

[3] Issues with blinding, but this is difficult to blind.

[4] Homogeneity is marginal, RRs are on both sides of the line of no effect. Larger studies have conflicting results.

[5] Findings from small studies and large studies differ.

[6] I2 statistic is 94%, desired is < 50%. Wide variability in the study findings.

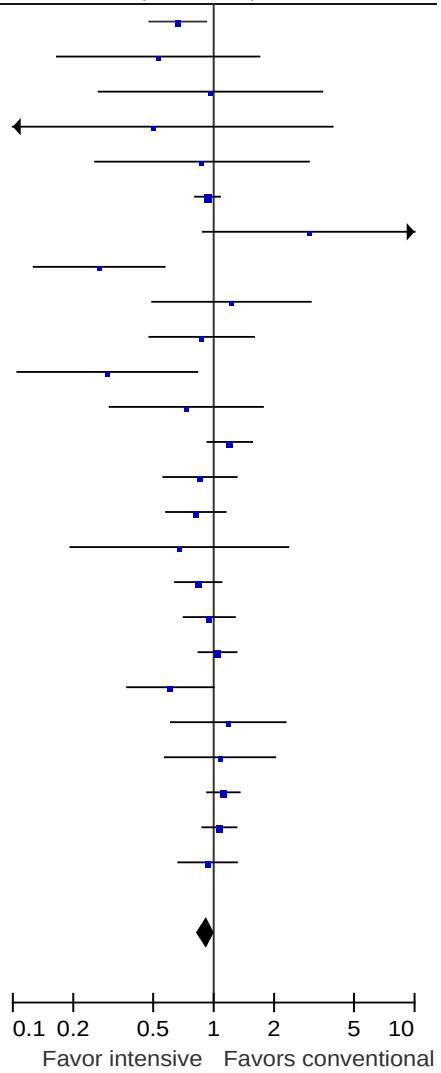
[7] CIs are wide

Glycemic Control, Outcome Mortality

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	55	765	85	783	5.9%	0.66 [0.48, 0.92]	2001
Grey 2004	4	34	6	27	0.8%	0.53 [0.17, 1.69]	2004
Yu 2005	4	28	4	27	0.6%	0.96 [0.27, 3.47]	2005
Bland 2005	1	5	2	5	0.3%	0.50 [0.06, 3.91]	2005
Henderson 2005	4	32	5	35	0.7%	0.88 [0.26, 2.98]	2005
Van den Berghe 2006	222	595	242	605	10.7%	0.93 [0.81, 1.08]	2006
Mitchell 2006	9	35	3	35	0.7%	3.00 [0.89, 10.16]	2006
Wang 2006	7	58	26	58	1.7%	0.27 [0.13, 0.57]	2006
McMullin 2007	6	11	4	9	1.2%	1.23 [0.49, 3.04]	2007
Oksanen 2007	12	39	18	51	2.5%	0.87 [0.48, 1.59]	2007
He 2007	7	150	6	38	1.0%	0.30 [0.11, 0.83]	2007
De Azevedo 2007	8	31	6	17	1.3%	0.73 [0.30, 1.76]	2007
Devos 2007	107	550	89	551	7.5%	1.20 [0.93, 1.55]	2007
Farah 2007	19	41	26	48	4.3%	0.86 [0.56, 1.30]	2007
Mackenzie 2008	39	121	47	119	5.6%	0.82 [0.58, 1.15]	2008
Zhang 2008	4	168	6	170	0.7%	0.67 [0.19, 2.35]	2008
Arabi 2008	72	266	83	257	7.2%	0.84 [0.64, 1.09]	2008
Brunkhorst 2008	61	247	75	289	6.6%	0.95 [0.71, 1.27]	2008
De La Rosa 2008	102	254	96	250	8.5%	1.05 [0.84, 1.30]	2008
He 2008	16	58	29	64	3.4%	0.61 [0.37, 1.00]	2008
Iapichino 2008	13	36	11	36	2.2%	1.18 [0.61, 2.28]	2008
Savioli 2009	14	45	13	45	2.3%	1.08 [0.57, 2.03]	2009
Finfer 2009	220	3010	197	3014	9.4%	1.12 [0.93, 1.35]	2009
Annane 2010	117	255	109	254	9.2%	1.07 [0.88, 1.30]	2010
Arabi 2011	42	120	45	120	5.7%	0.93 [0.67, 1.31]	2011
Total (95% CI)		**6954**		**6907**	**100.0%**	**0.91 [0.82, 1.02]**	
Total events	1165		1233				

Heterogeneity: Tau² = 0.02; Chi² = 40.37, df = 24 (P = 0.02); I² = 41%

Test for overall effect: Z = 1.65 (P = 0.10)

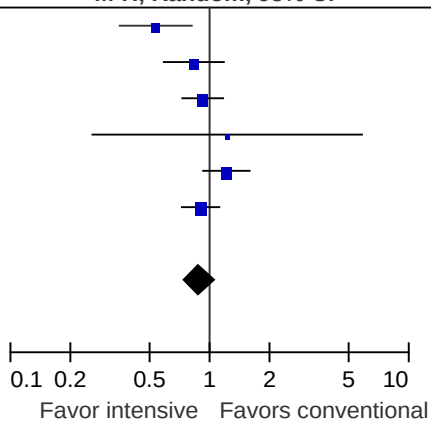


Glycemic Control, Outcome: Infectious Complication

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	32	765	61	783	13.7%	0.54 [0.35, 0.81]	2001
Grey 2004	21	34	20	27	16.7%	0.83 [0.59, 1.18]	2004
Farah 2007	30	41	38	48	22.9%	0.92 [0.73, 1.17]	2007
McMullin 2007	3	11	2	9	1.6%	1.23 [0.26, 5.82]	2007
De La Rosa 2008	84	254	68	250	21.0%	1.22 [0.93, 1.59]	2008
Arabi 2008	98	266	105	257	24.2%	0.90 [0.73, 1.12]	2008
Total (95% CI)		**1371**		**1374**	**100.0%**	**0.89 [0.73, 1.09]**	
Total events	268		294				

Heterogeneity: Tau² = 0.03; Chi² = 11.15, df = 5 (P = 0.05); I² = 55%

Test for overall effect: Z = 1.12 (P = 0.26)



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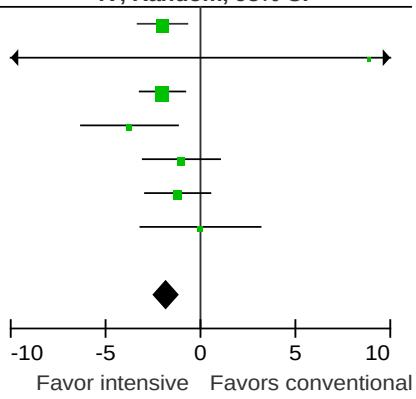
Glycemic Control, Outcome: ICU LOS

Study or Subgroup	Intensive control Mean	SD	Total	Conventional control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Van den Berghe 2001	7	11	765	9	15	783	27.6%	-2.00 [-3.31, -0.69]	2001
Grey 2004	33.4	68.3	34	24.5	19.4	27	0.1%	8.90 [-15.20, 33.00]	2004
Van den Berghe 2006	8	9	595	10	12	605	32.9%	-2.00 [-3.20, -0.80]	2006
Wang 2006	9.14	5.45	58	12.88	8.29	58	7.2%	-3.74 [-6.29, -1.19]	2006
Farah 2007	7	4.9	41	8	4.85	48	11.4%	-1.00 [-3.03, 1.03]	2007
Arabi 2008	9.6	8.5	266	10.8	11.3	257	16.0%	-1.20 [-2.92, 0.52]	2008
Arabi 2011	13.1	9.8	120	13.1	14.7	120	4.7%	0.00 [-3.16, 3.16]	2011
Total (95% CI)			**1879**			**1898**	**100.0%**	**-1.78 [-2.47, -1.09]**	

Heterogeneity: Tau² = 0.00; Chi² = 5.48, df = 6 (P = 0.48); I² = 0%

Test for overall effect: Z = 5.08 (P < 0.00001)

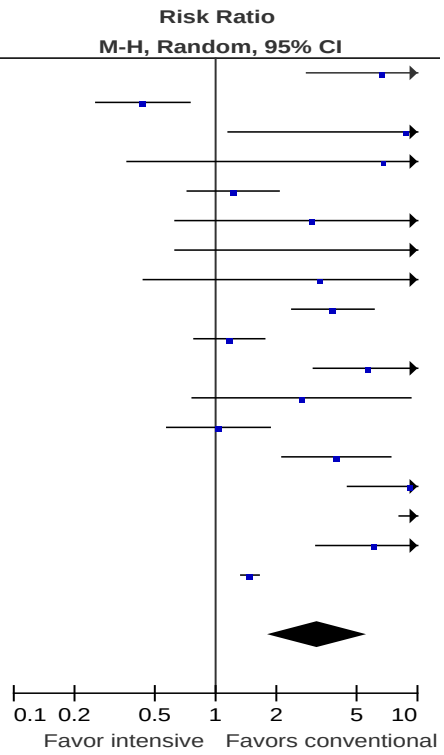


Glycemic Control, Outcome: Subjects with hypoglycemia

	Intensive control		Conventional control			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Van den Berghe 2001	39	765	6	783	6.0%	6.65 [2.83, 15.62]	2001
Grey 2004	11	34	20	27	6.6%	0.44 [0.26, 0.75]	2004
Henderson 2005	8	32	1	35	3.7%	8.75 [1.16, 66.15]	2005
Yu 2005	3	28	0	27	2.4%	6.76 [0.37, 124.98]	2005
Bland 2005	5	5	4	5	6.6%	1.22 [0.73, 2.06]	2005
Mitchell 2006	6	58	2	58	4.5%	3.00 [0.63, 14.25]	2006
Wang 2006	5	35	0	35	2.5%	11.00 [0.63, 191.69]	2006
McMullin 2007	4	11	1	9	3.7%	3.27 [0.44, 24.34]	2007
Farah 2007	80	550	21	551	6.6%	3.82 [2.40, 6.08]	2007
Devos 2007	23	41	23	48	6.7%	1.17 [0.78, 1.75]	2007
Mackenzie 2008	58	121	10	119	6.4%	5.70 [3.06, 10.62]	2008
Iapichino 2008	8	36	3	36	5.2%	2.67 [0.77, 9.25]	2008
De La Rosa 2008	21	254	20	250	6.5%	1.03 [0.57, 1.86]	2008
Brunkhorst 2008	42	247	12	280	6.4%	3.97 [2.14, 7.36]	2008
Arabi 2008	76	266	8	257	6.3%	9.18 [4.52, 18.63]	2008
Finfer 2009	206	3016	15	3014	6.6%	13.72 [8.15, 23.12]	2009
Savioli 2009	45	45	7	45	6.4%	6.07 [3.15, 11.68]	2009
Bilotta 2009	226	242	152	241	6.9%	1.48 [1.34, 1.64]	2009
Total (95% CI)		**5786**		**5820**	**100.0%**	**3.19 [1.81, 5.60]**	
Total events	866		305				

Heterogeneity: $Tau^2 = 1.19$; $Chi^2 = 305.40$, df = 17 ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: $Z = 4.03$ ($P < 0.0001$)



When should parenteral glutamine be utilized in the adult ICU patient?

Question: Should PN GLN vs Control be used for Critically Ill Patients?
Bibliography:

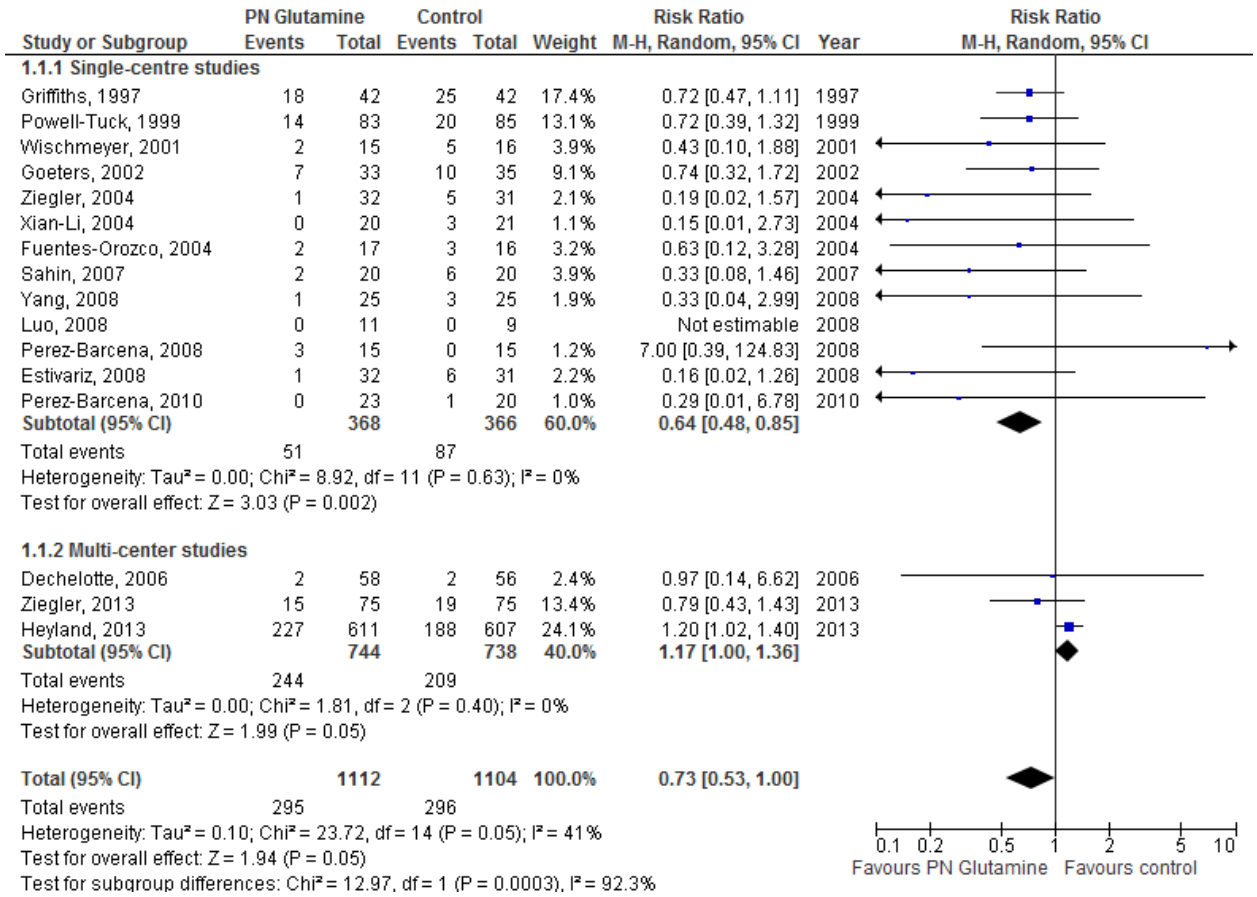
Griffiths 1997; Powell-Tuck 1999; Wischmeyer 2001; Fuentes-Orozco 2004; Xian-Li 2004; Palmese 2006; Tian 2006; Sahin 2007; Ozgultekin 2008; Estivariz 2008; Yang 2008; Cai 2008; Fuentes-Orozco 2008; Eroglu 2009; Perez-Barcena 2010; Cekman 2011; Wernerman 2011; Andrews 2011; grau 2011; Heyland 2013; Goeters 2002; Ziegler 2004; Perez-Barcena 2008; Dechelotte 2006; Duska 2008

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With PN GLN		Risk with Control	Risk difference with PN GLN (95% CI)
Hospital Mortality											
2216 (16studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	MODERATE[1] due to imprecision	295/1112 (26.5%)	296/1104 (26.8%)	RR 0.73 (0.53 to 1.0)	Study population	
										271 per 1000	68 fewer per 1000 (from 125 fewer to 14 more)

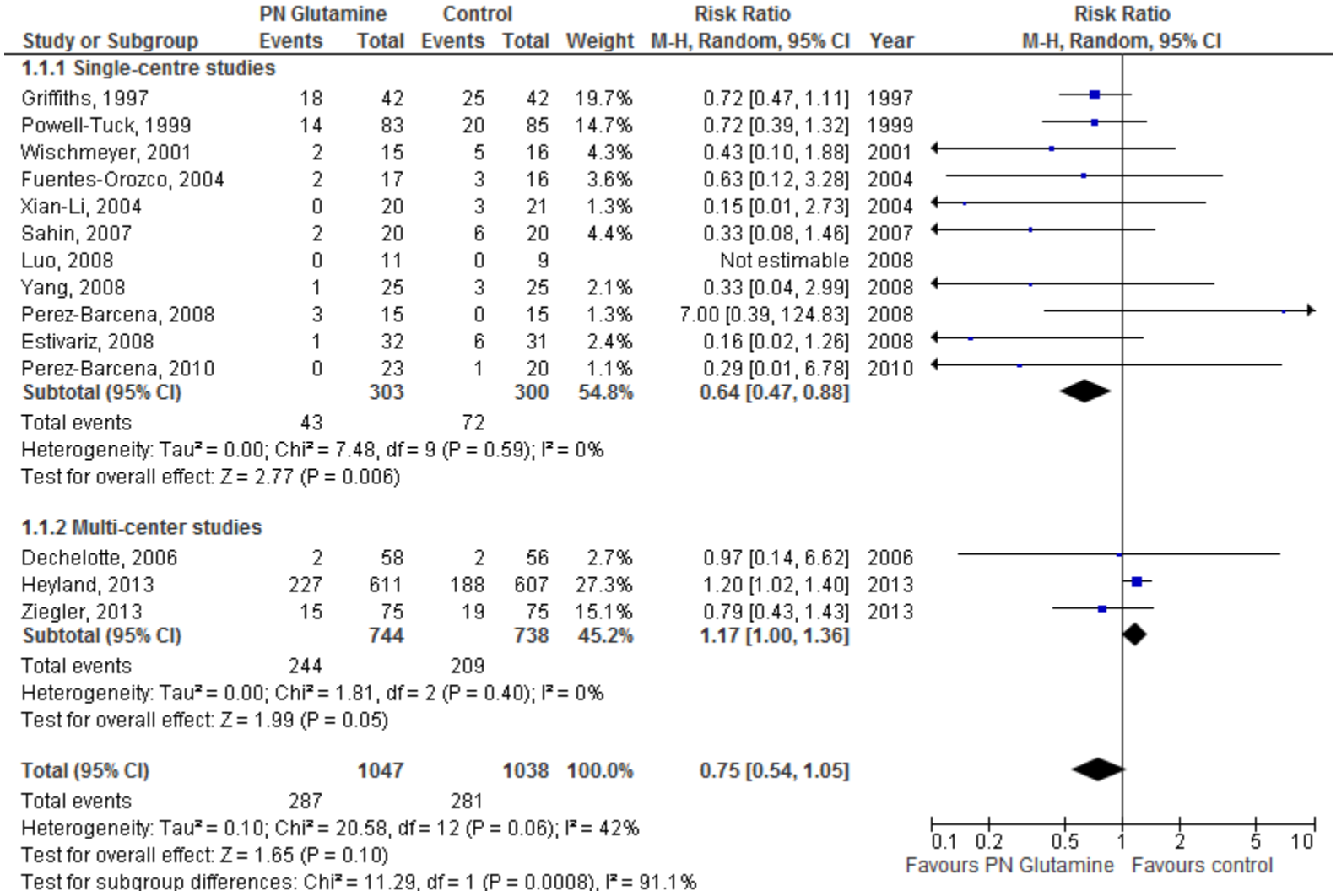
Infectious Complications											
1264 (12 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	MODERATE[1] due to imprecision	328/637 (51.5%)	297/627 (47.4%)	RR 0.86 (0.73 to 1.03)	Study population	
										515 per 1000	72 fewer per 1000 (from 139 fewer to 15 more)
VAP											
490 (6 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	MODERATE[1] due to imprecision	62/242 (25.6%)	46/248 (18.5%)	RR 0.75 (0.55 to 1.03)	Study population	
										256 per 1000	64 fewer per 1000 (from 115 fewer to 8 more)

[1]Wide confidence intervals

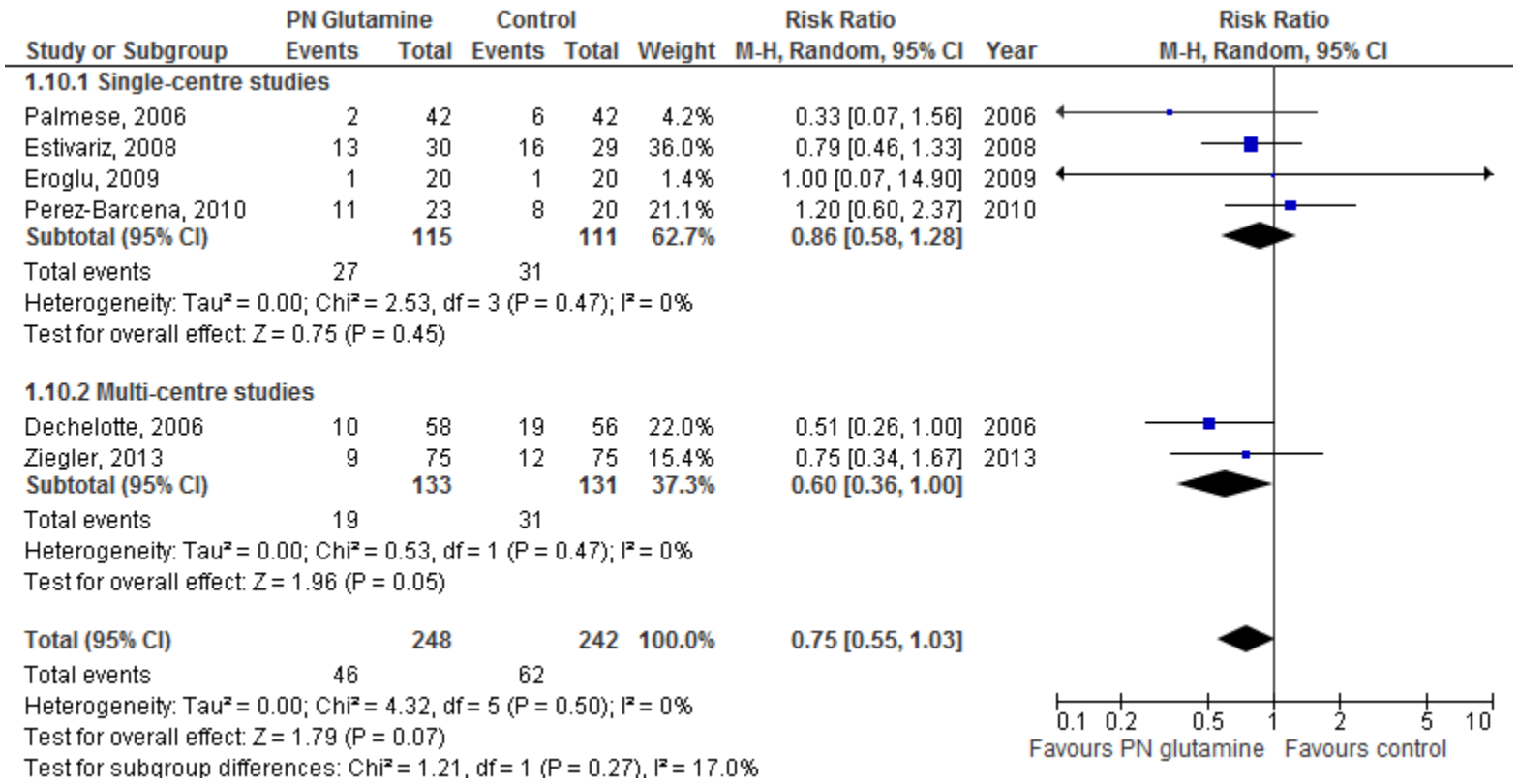
PN Glutamine vs Control, Outcome: Hospital Mortality



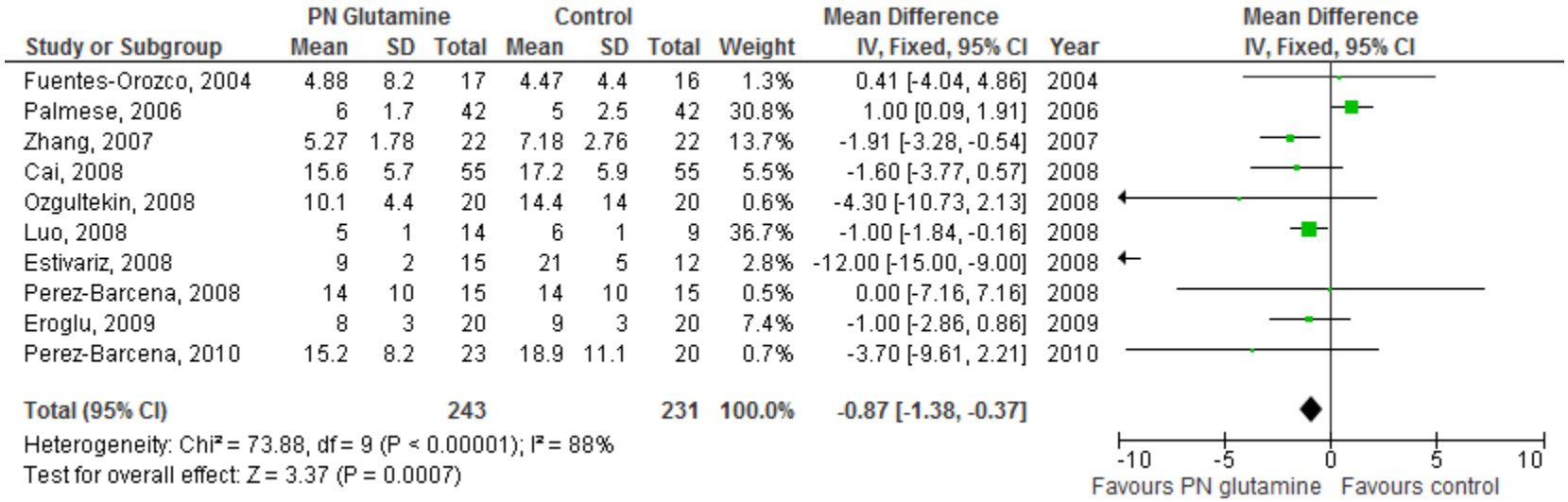
Parenteral Glutamine vs PN No Glutamine, Outcome: Infectious Complications



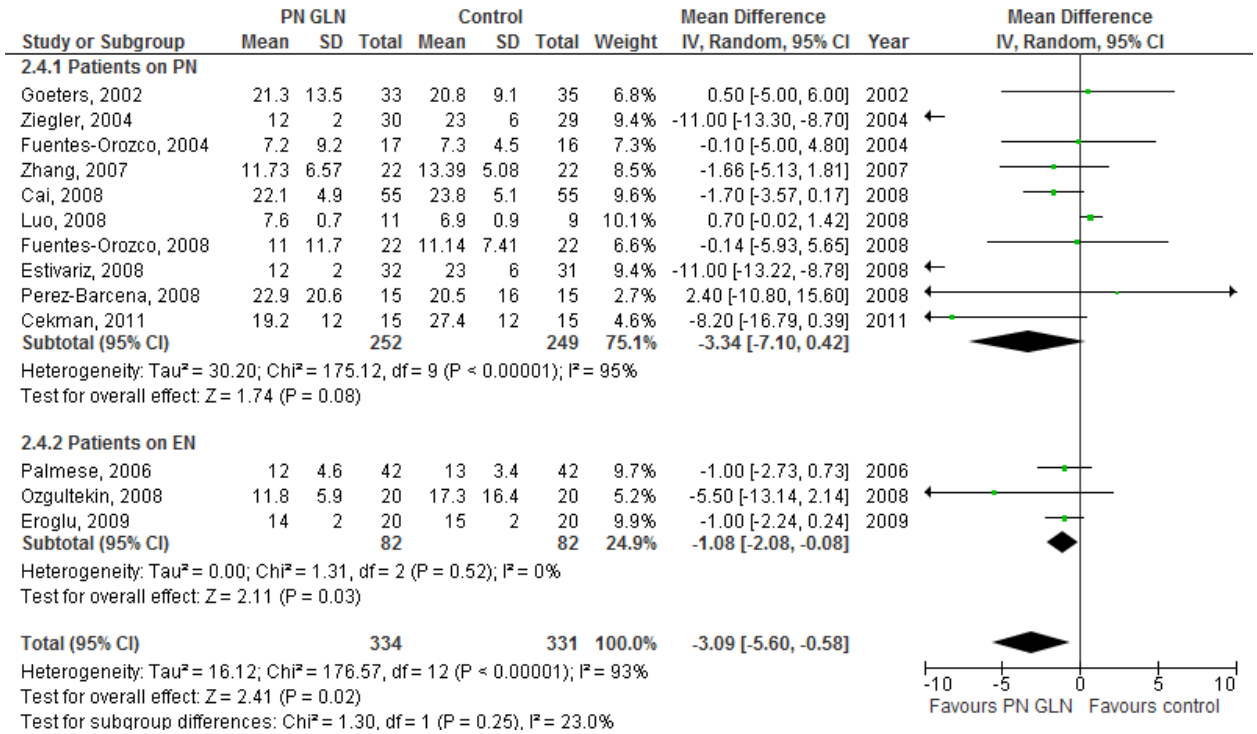
Parenteral Glutamine vs No Glutamine, Outcome: VAP



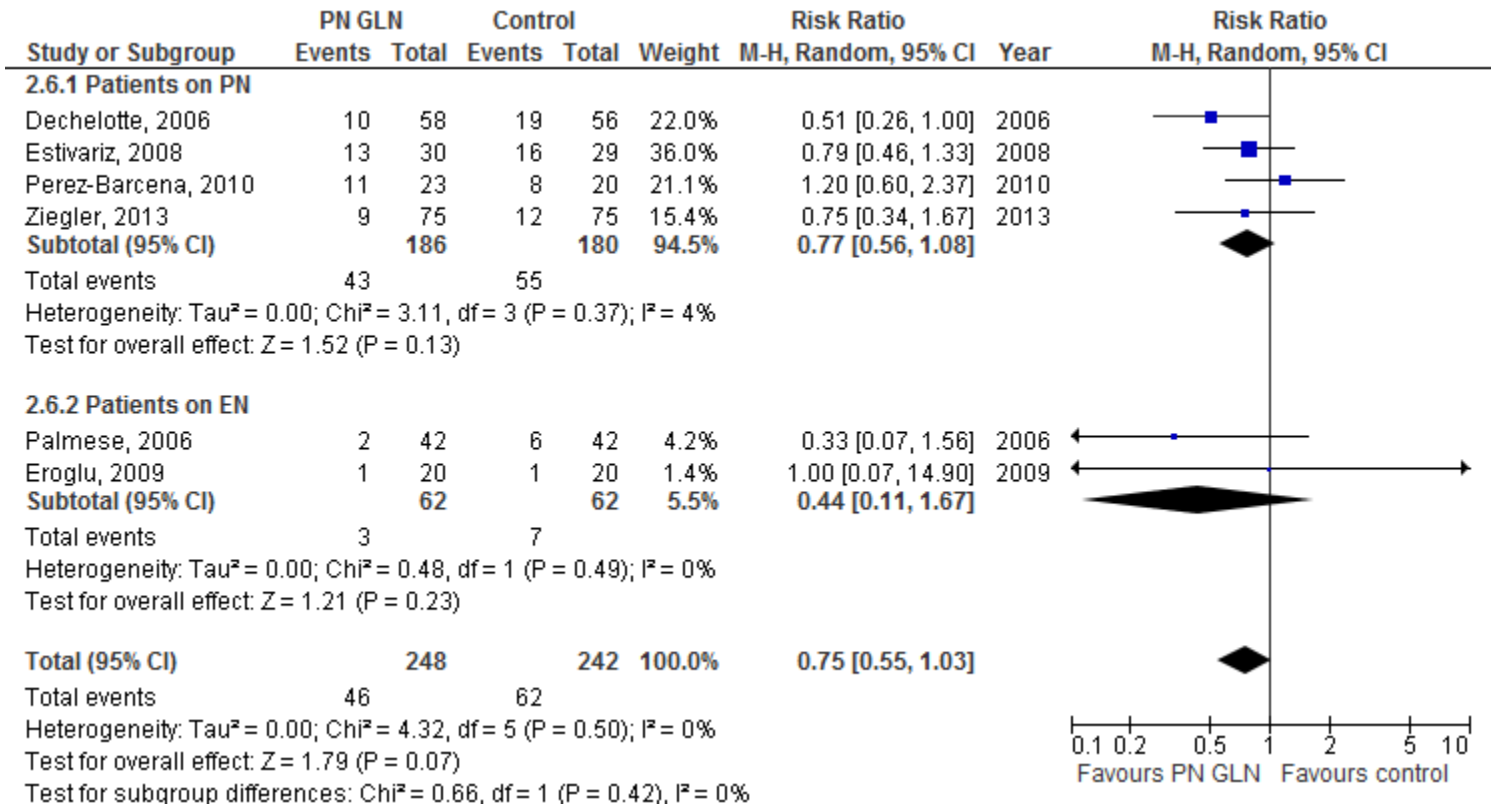
Parenteral Glutamine vs No Parenteral Glutamine, Outcome: Ventilator Days



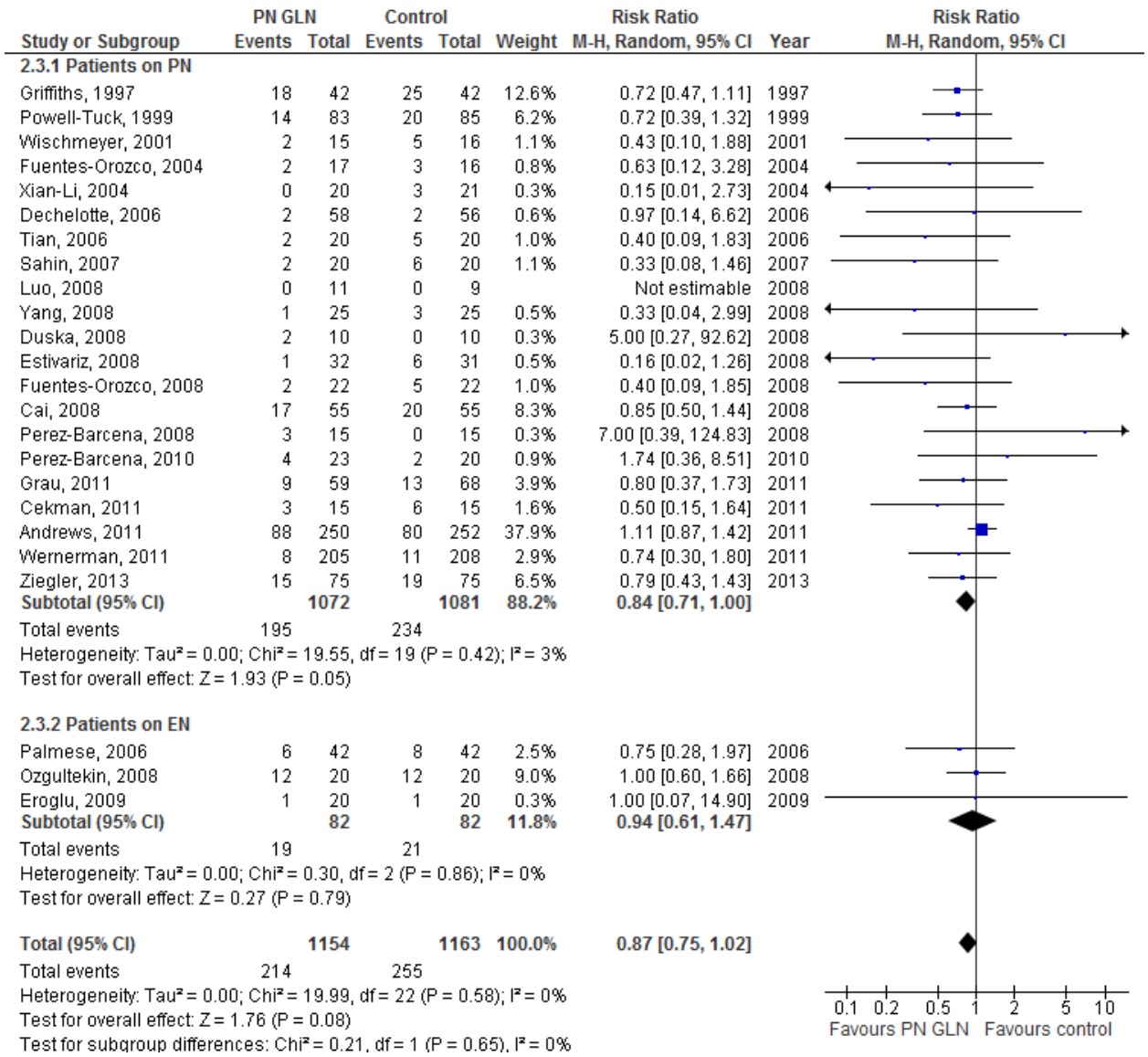
PN Gln vs PN No Gln; Outcome ICU LOS



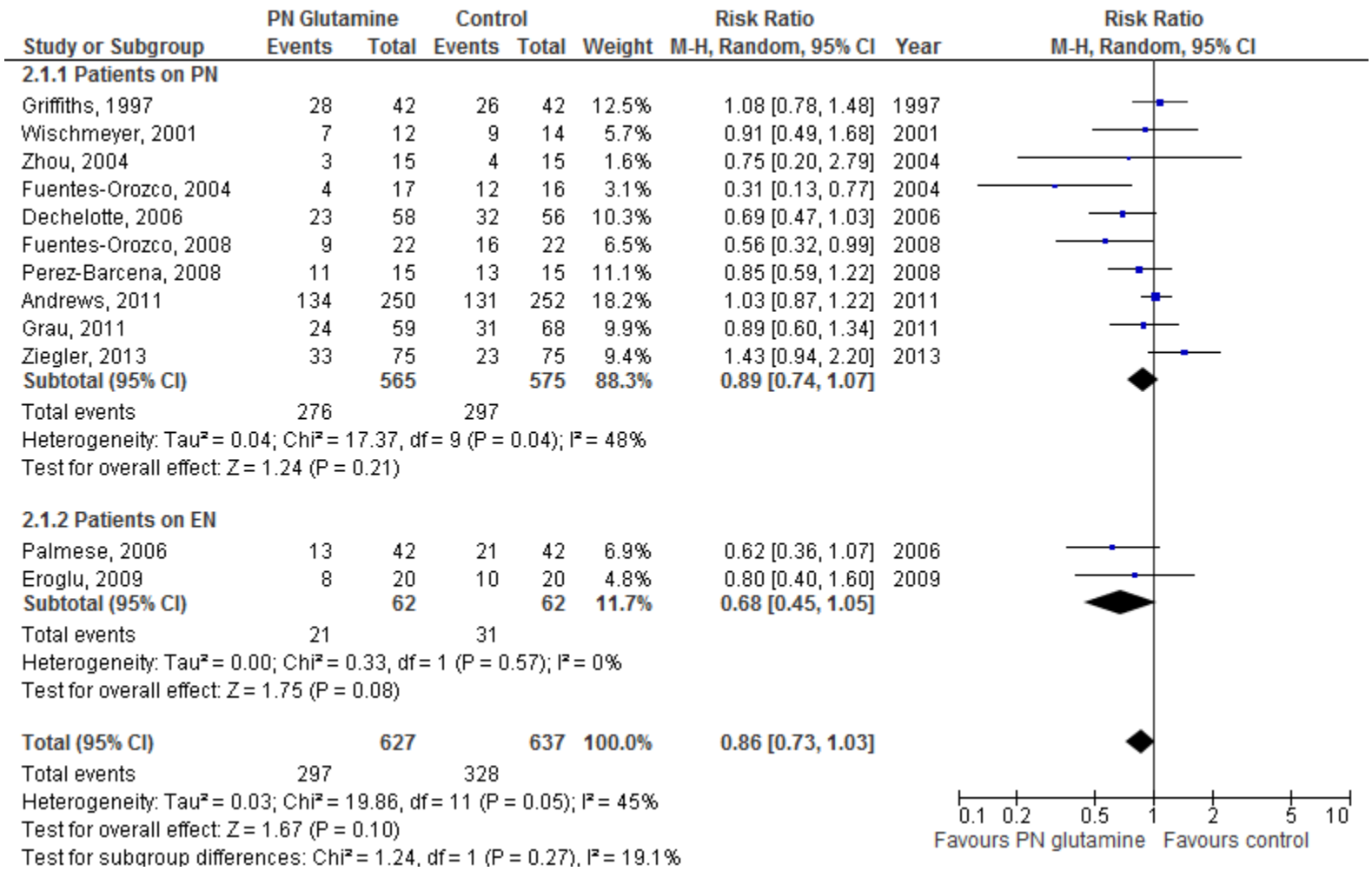
PN Gln vs PN No Gln; VAP rates



PN Gln vs No PN Gln; Outcome Mortality



PN Gln vs PN No Gln; Outcome Infectious Complications



High fat, low carbohydrate to manipulate respiratory quotient?

Question: I1:High fat/Low CHO vs. Standard for critically ill patients

Bibliography: Van den Berg, et al. 1994; Al Saady, et al., 1994; Mesejo, et al., 2003

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With STD (29-30% fat)	**With High fat formula (40% to 55% fat)**		**Risk with STD (29-30% fat)**	**Risk difference with High fat formula (40% to 55% fat)** (95% CI)
Mortality (CRITICAL OUTCOME)											
70 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	10/35 (28.6%)	11/35 (31.4%)	**RR 1.1** (0.54 to 2.25)	**286 per 1000**	**29 more per 1000** (from 131 fewer to 357 more)
Infections (CRITICAL OUTCOME)											
50 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	8/24 (33.3%)	10/26 (38.5%)	**RR 1.15** (0.55 to 2.43)	**333 per 1000**	**50 more per 1000** (from 150 fewer to 477 more)
LOS (Better indicated by lower values)											
50 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	24	26	-		The mean LOS in the intervention groups was **0 higher** (5.04 lower to 5.04 higher)

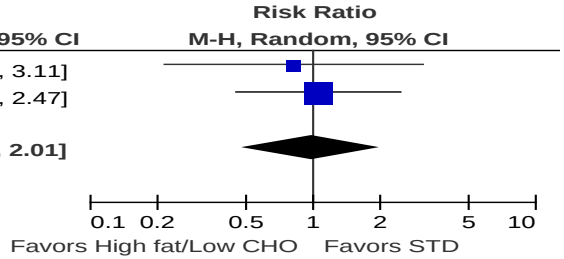
Ventilator Days (Better indicated by lower values)										
70 (2)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	35 35	-		The mean ventilator days in the intervention groups was **2.37 lower** (3.59 to 1.14 lower)

High Fat, Low Carb, Outcome: Mortality

Study or Subgroup	High fat/Low CHO Events	Total	STD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Al Saady 1994	3	11	3	9	28.8%	0.82 [0.22, 3.11]
Mesejo 2003	8	26	7	24	71.2%	1.05 [0.45, 2.47]
Total (95% CI)		**37**		**33**	**100.0%**	**0.98 [0.48, 2.01]**
Total events	11		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 0.05 (P = 0.96)

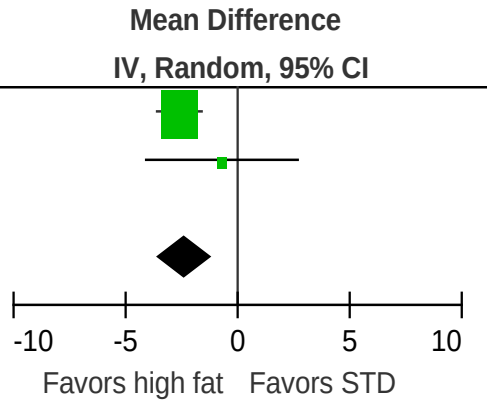


High Fat, Low Carb, Outcome: Ventilator days

Study or Subgroup	High Fat Mean	SD	Total	STD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
al Saady 1994	3.6	0.7	9	6.2	1.5	11	87.7%	-2.60 [-3.60, -1.60]
Mesejo 2003	8.7	6.2	26	9.4	6	24	12.3%	-0.70 [-4.08, 2.68]
Total (95% CI)			**35**			**35**	**100.0%**	**-2.37 [-3.59, -1.14]**

Heterogeneity: Tau² = 0.19; Chi² = 1.12, df = 1 (P = 0.29); I² = 10%

Test for overall effect: Z = 3.79 (P = 0.0002)



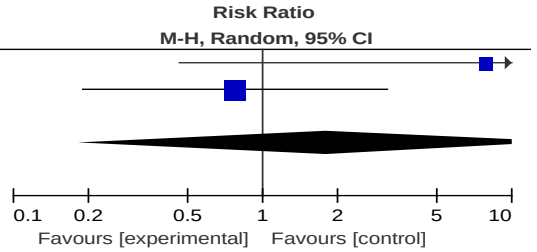
Do patients with mild acute pancreatitis need specialized nutrition therapy?

Volitional feeding vs. NPO or NJ feeding, Outcome: Complication (pain recurrence or pleural effusion, atelectasis, or fluid collection

	Volitional feeding		NPO or NJ feeding			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Pandey 2004	4	15	0	13	36.6%	7.88 [0.46, 133.76]	2004
Eckerwall 2007	3	29	4	30	63.4%	0.78 [0.19, 3.17]	2007
Total (95% CI)		**44**		**43**	**100.0%**	**1.81 [0.18, 17.82]**	
Total events	7		4				

Heterogeneity: Tau² = 1.63; Chi² = 2.25, df = 1 (P = 0.13); I² = 56%

Test for overall effect: Z = 0.51 (P = 0.61)



Should an oral soft diet, per patient's tolerance vs. clear liquid diet be used for mild acute pancreatitis?

Question L1c: Should an oral soft diet, per patient's tolerance vs. clear liquid diet be used for mild acute pancreatitis?

Bibliography: Li JY, Yu T, Chen GC, et al. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: A meta-analysis. PLoS One. 2013;8(6):e64926. Includes 11 studies including Wu 2008; Petrov 2006; Eckerwall 2006 Gupta 2003; Olah 2002; Qin 2008; Bakker 2009; McClave 1997; Kalfarentzos 1997; Olah 1996; Vieira 2010

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Clear liquid diet	**With An oral soft diet, per patient's tolerance**		**Risk with Clear liquid diet**	**Risk difference with An oral soft diet, per patient's tolerance** (95% CI)
Infection Complications (CRITICAL OUTCOME; assessed with: number of all infections (RCT only))											
282 (8 studies)	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1,2] due to risk of bias	37/147 (25.2%)	17/135 (12.6%)	**OR 0.38** (0.21 to 0.77)	**252 per 1000**	**138 fewer per 1000** (from 46 fewer to 186 fewer)
Infectious complications subjects with pSAP or SAP (CRITICAL OUTCOME; assessed with: number of all infections (RCT only)											
278 (4 studies)	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1,3] due to risk of bias	62/142 (43.7%)	30/136 (22.1%)	**HR 0.32** (0.17 to 0.53)	**437 per 1000**	**269 fewer per 1000**

										(from 174 fewer to 344 fewer)
Catheter related septic complications (CRITICAL OUTCOME; assessed with: number of catheter related complications (RCT only))										
230 (5 studies)	serious	no serious inconsistency[2]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[2] due to risk of bias	13/117 (11.1%)	5/113 (4.4%)	**OR 0.23** (0.09 to 0.57)	**111 per 1000**	**83 fewer per 1000** (from 45 fewer to 100 fewer)
Catheter related septic complication (assessed with: number of catheter related complications in pSAP or SAP (RCT only))										
214 (4 studies)	serious	no serious inconsistency	no serious indirectness	serious[4]	undetected	**LOW**[4] due to risk of bias, imprecision	21/101 (20.8%)	5/113 (4.4%)	**OR 0.23** (0.09 to 0.61)	**208 per 1000**	**151 fewer per 1000** (from 70 fewer to 185 fewer)
Organ failure rate (IMPORTANT OUTCOME; assessed with: Count of organ failure (RCT only))										
225 (5 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1] due to risk of bias	49/116 (42.2%)	20/109 (18.3%)	**OR 0.28** (0.14 to 0.54)	**422 per 1000**	**252 fewer per 1000** (from 139 fewer to 330 fewer)

[1] Blinding of participants, personnel or outcome assessors was not done in 7/8 (87%)studies.

[2] Heterogeneity is zero, but all infections are included, CLABSI, VAP, and UTI.

[3] I2 statistic for heterogeneity is 50%
[4] Low number of events in included studies

No Forest Plots: Meta-analyses only were synthesized.

Should immune enhancing formula vs. standard enteral formula be used in acute pancreatitis?

Question: Should immune enhancing formula vs. standard enteral formula be used in acute pancreatitis?

Bibliography: Petrov 2011

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard enteral formula	**With Immune enhancing formula**		**Risk with Standard enteral formula**	**Risk difference with Immune enhancing formula** (95% CI)
Infectious complication (CRITICAL OUTCOME; assessed with: count)											
78 (3 studies)	serious[1]	serious[2]	no serious indirectness	serious[3]	undetected	**VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	14/38 (36.8%)	12/40 (30%)	**RR 0.818** (0.436 to 1.533)	**368 per 1000**	**67 fewer per 1000** (from 208 fewer to 196 more)
Mortality (CRITICAL OUTCOME; assessed with: Count)											
76 (3 studies)	serious[1]	serious[2]	no serious indirectness	serious	undetected	**VERY LOW**[1,2] due to risk of bias, inconsistency, imprecision	7/36 (19.4%)	4/40 (10%)	**RR 0.6439** (0.2003 to 2.0693)	**194 per 1000**	**69 fewer per 1000** (from 155 fewer to 208 more)

[1] Poor methods across studies, No blinding, allocation concealment poorly reported.
[2] Used outcome measures we are recommending practitioners not use in another section of the guideline
[3] Very low number of subjects

No Forest Plots; a synthesis of a MA.

Should PN vs EN be used for pancreatitis?

Should PN vs EN be used for pancreatitis?

Bibliography: WAbou- Assi 2002; Eckerwall 2006; Kalfarentzos 1997; McClave 1997; Ohlah 2002; Petrov 2006; Windsor 1998

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Post pyloric EN	**With PN**		**Risk with Post pyloric EN**	**Risk difference with PN** (95% CI)
Mortality (CRITICAL OUTCOME)											
342 (9 studies)	very serious[1]	serious[2,3]	no serious indirectness	serious[4]	undetected	**VERY LOW**[1,2,3,4] due to risk of bias, inconsistency, imprecision	10/165 (6.1%)	27/177 (15.3%)	**RR 2.17** (1.13 to 4.17)	**61 per 1000**	**71 more per 1000** (from 8 more to 192 more)
Hosptial LOS (CRITICAL OUTCOME; Better indicated by lower values)											
85 (2 studies)	serious[1]	serious[2,3]	no serious indirectness[5]	serious[6]	undetected	**VERY LOW**[1,2,3,5,6] due to risk of bias, inconsistency, imprecision	43	42	**-**	The mean hosptial los ranged across control groups from **79.7-14.2 days**	The mean hosptial los in the intervention groups was **3.26 higher** (1.31 to 5.22 higher)
Complications (CRITICAL OUTCOME)											
128 (4 studies)	serious[1]	serious[2,3]	no serious indirectness	serious[4]	undetected	**VERY LOW**[1,2,3,4] due to risk of bias, inconsistency, imprecision	32/68 (47.1%)	27/60 (45%)	**RR 1.02** (0.39 to 2.69)	**471 per 1000**	**9 more per 1000** (from 287 fewer to 795 more)

Infections (CRITICAL OUTCOME)										
246 (7 studies)	serious[7]	serious[2,3]	no serious indirectness	no serious imprecision	undetected	**LOW**[2,3,7] due to risk of bias, inconsistency	20/124 (16.1%)	52/122 (42.6%)	**RR 2.45** (1.61 to 3.74)	**161290 per 1000000**	**233871 more per 1,000,000** (from 98387 more to 441935 more)

[1] None of the studies were blinded
[2] Most studies fed into the jejunum, but some fed into the duodenum
[3] Formula types varied
[4] Small number of subjects and small number of events
[5] Older studies, uncertain if deaths in any group decreased LOS. Better outcome to report is days to discharge alive.
[6] Various definitions of complications were used
[7] No explanation was provided

Should nasogastric feeding tube placement vs. nasojejunal tube placement be used for acute pancreatitis?

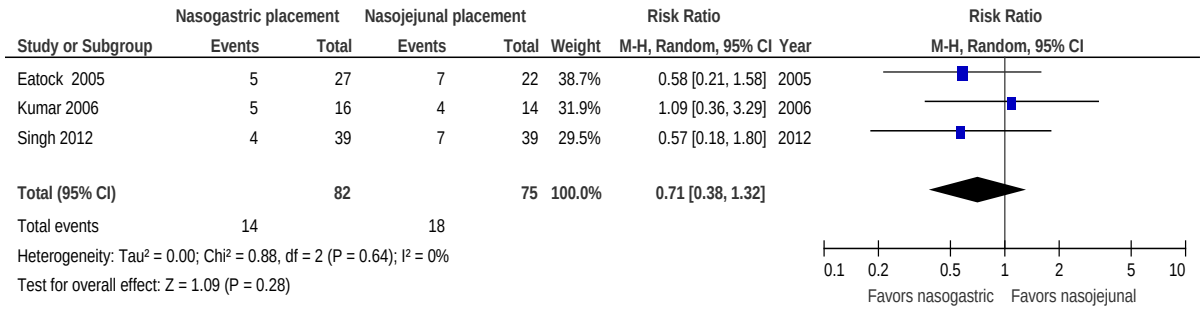
Question: Should nasogastric feeding tube placement vs. nasojejunal tube placement be used for acute pancreatitis?

Bibliography: Meta-analysis by Chang 2013. Included studies Eatock 2005; Kumar 2006 and Singh 2012

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Nasojejunal tube placement	**With Nasogastric feeding tube placement**		**Risk with Nasojejunal tube placement**	**Risk difference with Nasogastric feeding tube placement** (95% CI)
Mortality (CRITICAL OUTCOME)											
157 (3 studies)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**VERY LOW**[1,2] due to risk of bias, imprecision	18/75 (24%)	14/82 (17.1%)	**RR 0.71** (0.38 to 1.32)	**240 per 1000**	**70 fewer per 1000** (from 149 fewer to 77 more)
Tracheal aspiration (CRITICAL OUTCOME)											
108 (2 studies)	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**VERY LOW**[1,2,3] due to risk of bias, imprecision	7/53 (13.2%)	3/55 (5.5%)	**RR 0.46** (0.14 to 1.55)	**132 per 1000**	**71 fewer per 1000** (from 114 fewer to 73 more)

Exacerbation of pain (CRITICAL OUTCOME)											
66 (3 studies)	very serious[1,3]	no serious inconsistency[4]	no serious indirectness	serious[2,4,5]	undetected	**VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision	5/39 (12.8%)	2/27 (7.4%)	**RR 0.84** (0.27 to 2.59)	**128 per 1000**	**21 fewer per 1000** (from 94 fewer to 204 more)
Diarrhea (CRITICAL OUTCOME)											
157 (3 studies)	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**VERY LOW**[1,2,3] due to risk of bias, imprecision	7/75 (9.3%)	11/82 (13.4%)	**RR 1.39** (0.57 to 3.36)	**93 per 1000**	**36 more per 1000** (from 40 fewer to 220 more)

Nasogastric vs. Nasojejunal placement; Outcome Mortality

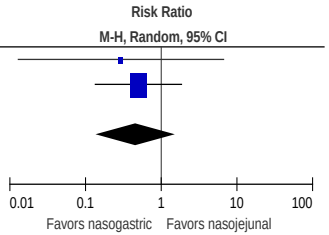


Nasogastric vs. Naso-jejunal placement; Outcome Tracheal aspiration

Study or Subgroup	Nasogastric placement Events	Total	Nasojejunal placement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kumar 2006	0	16	1	14	15.0%	0.29 [0.01, 6.69]	2006
Singh 2012	3	39	6	39	85.0%	0.50 [0.13, 1.86]	2012
Total (95% CI)		**55**		**53**	**100.0%**	**0.46 [0.14, 1.55]**	
Total events	3		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%

Test for overall effect: Z = 1.25 (P = 0.21)

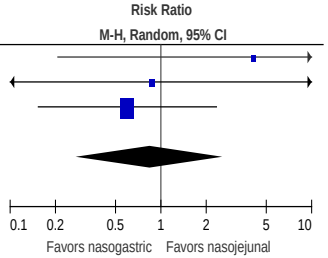


Nasogastric vs. Naso-jejunal placement; Outcome Exacerbation of pain

Study or Subgroup	Nasogastric placement Events	Total	Nasojejunal placement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Eatock 2005	2	27	0	22	14.2%	4.11 [0.21, 81.33]	2005
Kumar 2006	1	16	1	14	17.6%	0.88 [0.06, 12.73]	2006
Singh 2012	3	39	5	39	68.2%	0.60 [0.15, 2.34]	2012
Total (95% CI)		**82**		**75**	**100.0%**	**0.84 [0.27, 2.59]**	
Total events	6		6				

Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%

Test for overall effect: Z = 0.30 (P = 0.76)

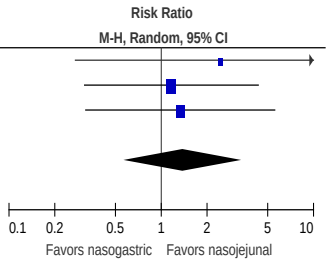


Nasogastric vs. Naso-jejunal placement; Outcome Diarrhea

Study or Subgroup	Nasogastric placement Events	Total	Nasojejunal placement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Eatock 2005	3	27	1	22	16.3%	2.44 [0.27, 21.89]	2005
Kumar 2006	4	16	3	14	45.4%	1.17 [0.31, 4.34]	2006
Singh 2012	4	39	3	39	38.3%	1.33 [0.32, 5.57]	2012
Total (95% CI)		**82**		**75**	**100.0%**	**1.39 [0.57, 3.36]**	
Total events	11		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%

Test for overall effect: Z = 0.72 (P = 0.47)



Should probiotics be used in pancreatitis?

Should probiotics be used in pancreatitis?

Bibliography: Zhang 2010 (meta analysis) Includes Olah, 2002; Olah 2007; Karakan 2007; Qin 2008; Besselink 2008; Li 2007 & Wu 2009

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Probiotics**		**Risk with Control**	**Risk difference with Probiotics** (95% CI)
Infectious morbidity (CRITICAL OUTCOME)											
507 (4 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	undetected[4]	⨁⨁⨀⨀ **LOW**[1,2,3,4] due to inconsistency, imprecision	107/249 (43%)	73/258 (28.3%)	**OR 0.3** (0.09 to 1.02)	**430 per 1000**	**245 fewer per 1000** (from 366 fewer to 5 more)
Mortality (CRITICAL OUTCOME)											
507 (5 studies)	no serious risk of bias[1]	serious[5]	no serious indirectness	serious[3]	undetected	⨁⨁⨀⨀ **LOW**[1,3,5] due to inconsistency, imprecision	21/249 (8.4%)	29/258 (11.2%)	**RR 0.73** (0.18 to 2.98)	**84 per 1000**	**23 fewer per 1000** (from 69 fewer to 167 more)
LOS Hospital (CRITICAL OUTCOME; range of scores: 10-45; Better indicated by lower values)											
378 (4 studies)	serious[6]	serious[7,8]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[6,7,8] due to risk of	183	195	-	The mean los hospital in the control groups was **24.7 d**	The mean los hospital in the

						bias, inconsistency				intervention groups was **3.87 lower** (6.2 to 1.54 lower)

[1] Jadad scores are > 3 but allocation was not concealed, and it is unclear if randomization occured or if all subjects randomized were inlcuded in the analysis

[2] I2 Statistic is 84% (the range of values is 0-100; < 50% is desirable)

[3] Small sample sizes in the included studies

No forest plots; meta analysis synthesis only.

Should early EN vs STD nutrition be used for trauma patients?

Should early enteral nutrition vs. standard enteral nutrition be used for trauma patients?

Bibliography: Doig 2010 (meta-analysis) Included studies: Kompan 1999; Kompan 2004 & Chuntrasakul 1996

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard enteral nutrition	**With Early enteral nutrition**		**Risk with Standard enteral nutrition**	**Risk difference with Early enteral nutrition** (95% CI)
Mortality (CRITICAL OUTCOME; assessed with: number of deaths)											
126 (3 studies)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected[2]	**VERY LOW**[1,2] due to risk of bias, imprecision	6/61 (9.8%)	1/65 (1.5%)	**RR 0.2** (0.04 to 0.91)	**Study population**	
										98 per 1000	**79 fewer per 1000** (from 9 fewer to 94 fewer)
										Moderate	
											-

[1] Low number of subjects and low number of events

[2] To few included studies to assess a funnel plot

Should immunonutrition vs STD be used in trauma patients?

Should Immunonutrition vs. standard be used in trauma patients?

Bibliography: Marik 2008 (meta analysis) Included studies: Brown 1994; Engel 1997; Moore, 1994; Kudsk 1996; Mendez 1997; Weiman 1998; Tsuei 2005

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard	**With Immunonutrition**		**Risk with Standard**	**Risk difference with Immunonutrition** (95% CI)
Mortality (CRITICAL OUTCOME)											
300 (7 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected[3]	**LOW**[1,2,3] due to risk of bias, imprecision	13/145 (9%)	13/155 (8.4%)	**RR 1.03** (0.4 to 2.65)	**90 per 1000**	**3 more per 1000** (from 54 fewer to 148 more)
Infections (CRITICAL OUTCOME)											
372 (8 studies)	serious[1]	serious[4]	no serious indirectness	serious[5]	undetected[3]	**VERY LOW**[1,3,4,5] due to risk of bias, inconsistency, imprecision	81/182 (44.5%)	68/190 (35.8%)	**RR 0.72** (0.27 to 1.91)	**445 per 1000**	**125 fewer per 1000** (from 325 fewer to 405 more)
LOS Hospital (CRITICAL OUTCOME; range of scores: 14.6-70.2; Better indicated by lower values)											
227 (5 studies)	serious[1]	serious[6]	serious[7]	serious[5]	undetected[3]	**VERY LOW**[1,3,5,6,7] due to risk of bias, inconsistency, indirectness, imprecision	109	118	-	The mean los hospital in the control groups was **31 days**	The mean los hospital in the intervention groups was **3.07 lower** (6.64 lower to 0.51 higher)

[1] Blinding of participants, providers and or outcome assessors is not reported
[2] Small sample sizes and small number of events

[3] Too few studies to assess a funnel plot for publication bias
[4] I2 statistic is 70% (range 0-100, less than 50% is desired)
[5] Confidence intervals of the included studies are wide
[6] I2 statistic is 78% (range 0-100%, less than 50% is desirable)
[7] It is not certain how mortality affects the LOS outcome

Should PN vs. EN be used for head injured patients?

Should parenteral vs enteral be used for head injured patients?

Bibliography: Perel 2006 (meta-analysis) Studies included in the meta analysis:

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Enteral	**With Parenteral**		**Risk with Enteral**	**Risk difference with Parenteral** (95% CI)
Mortality at the end of follow-up (CRITICAL OUTCOME)											
229 (6 studies)	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	32/119 (26.9%)	20/110 (18.2%)	**RR 0.71** (0.41 to 1.25)	**269 per 1000**	**78 fewer per 1000** (from 159 fewer to 67 more)
Poor outcome at the end of follow-up (CRITICAL OUTCOME)											
83 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⨁⨀⨀ **LOW**[1,3] due to risk of bias, imprecision	18/39 (46.2%)	14/44 (31.8%)	**RR 0.69** (0.4 to 1.19)	**462 per 1000**	**143 fewer per 1000** (from 277 fewer to 88 more)

[1] In the Perel 2006 meta analysis, only allocation concealment was assessed. Included studies were assess to have either inadequate or unclear allocation concealment.

[2] The I2 statistic is 30 (range 0-100%, desired is < 50%)

[3] Small sample sizes and small number of events..

EN vs PN in Sepsis

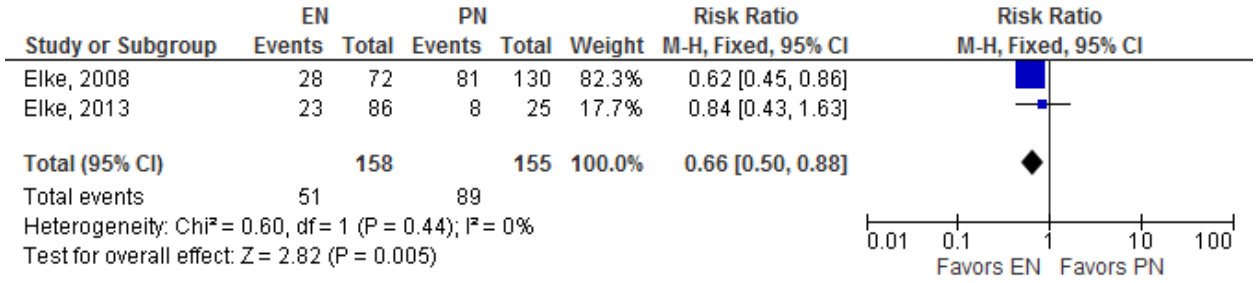
EN vs PN in ICU Patients with Sepsis

Bibliography: Elke 2008; Elke 2013e

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Mortality in Patients with Sepsis**		**Risk with Control**	**Risk difference with Mortality in Patients with Sepsis** (95% CI)
Mortality											
313 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	**VERY LOW**[1] due to risk of bias	89/155 (57.4%)	51/158 (32.3%)	**RR 0.66** (0.5 to 0.88)	**Study population**	
										574 per 1000	**195 fewer per 1000** (from 69 fewer to 287 fewer)

[1] Studies were not set up to address septic patients only, these are post hoc analyses.

Figure. EN vs. PN in Patients with Sepsis, Outcome: Mortality



Selenium and Antioxidants in Sepsis

Question: Parenteral Selenium in Sepsis, Outcomes Mortality and Infections

Bibliography: Angstwurm 1999; Angstwurm 2007; Forceville 2007; Gonzalez 2009; Heyland 2013; Manzanares 2011; Mishra 2007; Valenta 2011; Zimmerman 1997

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Parenteral Selenium in Sepsis, Outcome Mortality**		**Risk with Control**	**Risk difference with Parenteral Selenium in Sepsis, Outcome Mortality** (95% CI)
Mortality											
1888 (9 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	**MODERATE** due to imprecision	344/940 (36.6%)	325/948 (34.3%)	**RR 0.94** (0.83 to 1.06)	**Study population**	
										366 per 1000	**22 fewer per 1000** (from 62 fewer to 22 more)
1249 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	**MODERATE** due to imprecision			**RR 0.85** (0.66 to 1.08)		

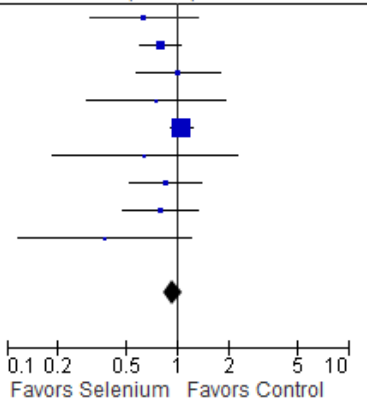
[1] The finding is imprecise because the combined effect is not statistically significant.

PN Selenium in Patients with Sepsis, Outcome Mortality

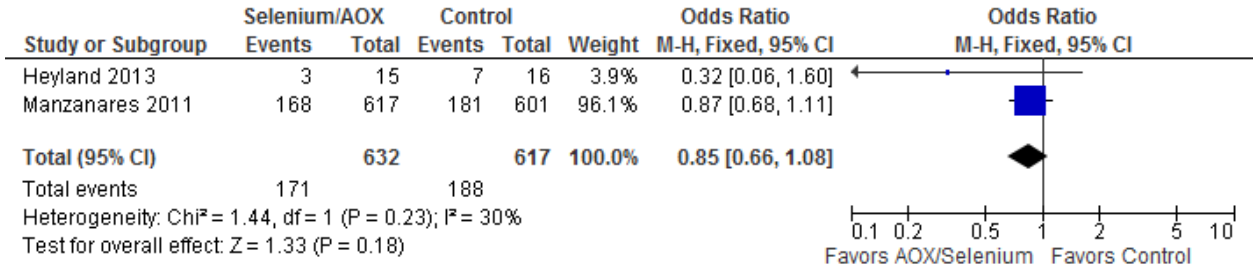
Study or Subgroup	Parenteral Selenium Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Angstwurm 1999	7	21	11	21	3.2%	0.64 [0.31, 1.32]
Angstwurm 2007	46	116	61	122	17.3%	0.79 [0.60, 1.06]
Forceville 2007	14	31	13	29	3.9%	1.01 [0.58, 1.76]
González 2009	6	34	8	34	2.3%	0.75 [0.29, 1.93]
Heyland 2013	216	617	199	601	58.6%	1.06 [0.90, 1.24]
Manzanares 2011	3	15	5	16	1.4%	0.64 [0.18, 2.22]
Mishra 2007	11	19	15	22	4.0%	0.85 [0.53, 1.37]
Valenta 2011	19	75	24	75	7.0%	0.79 [0.48, 1.32]
Zimmerman 1997	3	20	8	20	2.3%	0.38 [0.12, 1.21]
Total (95% CI)		**948**		**940**	**100.0%**	**0.94 [0.83, 1.06]**
Total events	325		344			

Heterogeneity: $Chi^2 = 8.23$, $df = 8$ ($P = 0.41$); $I^2 = 3\%$

Test for overall effect: $Z = 0.99$ ($P = 0.32$)



PN Selenium vs Control in Patients with Sepsis



Should early EN vs. STD be used for elective gastrointestinal surgery?

There are **no forest plots** as this is a GRADE of a completed meta-analysis.

Question: Should early EN vs. STD be used for elective gastrointestinal surgery?

Bibliography: Osland, E. Yunus, R. M., Khan, S., & Memon, A.S. 2011. Early versus tradition a postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN, 35, 4, 473-787. doi 10.1177/0148607110385698

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With STD	**With Early EN**		**Risk with STD**	**Risk difference with Early EN** (95% CI)
Complications (excluding mortality and nausea and vomiting) All years C (CRITICAL OUTCOME)											
1238 (15 studies) 5.2-24.5 days	serious[1]	serious[2]	serious[3]	serious[4,5]	reporting bias strongly suspected[6]	**VERY LOW**[1,2,3,4,5,6] due to risk of bias, inconsistency, indirectness, imprecision, publication bias	191/616 (31%)	113/622 (18.2%)	**OR 0.53** (0.33 to 0.86)	**310 per 1000**	**118 fewer per 1000** (from 31 fewer to 181 fewer)
Complications (excluding mortality, nausea, vomiting) Pre 2000 Osland (CRITICAL OUTCOME)											
607 (10 studies) 5.2-24.5 days	serious[1]	serious[2]	serious[3]	serious[4,5]	reporting bias strongly suspected[6]	**VERY LOW**[1,2,3,4,5,6] due to risk of bias, inconsistency, indirectness, imprecision, publication bias	78/304 (25.7%)	48/303 (15.8%)	**OR 0.53** (0.32 to 0.89)	**257 per 1000**	**102 fewer per 1000** (from 22 fewer to 157 fewer)
Complications (excluding mortality, nausea, vomiting) Post 2000 Osland (CRITICAL OUTCOME)											

1240 (5 studies) 5.2-24.5 days	serious[1]	serious[2]	serious[3]	serious[4,5]	reporting bias strongly suspected[6]	**VERY LOW**[1,2,3,4,5,6] due to risk of bias, inconsistency, indirectness, imprecision, publication bias	192/617 (31.1%)	114/623 (18.3%)	**OR 0.53** (0.33 to 0.86)	**311 per 1000**	**118 fewer per 1000** (from 31 fewer to 181 fewer)
Mortality All Years Osland (CRITICAL OUTCOME)											
1240 (15 studies) 5.2-24.5 days	serious[1]	no serious inconsistency[7]	no serious indirectness	very serious[8]	undetected	**VERY LOW**[1,7,8] due to risk of bias, imprecision	11/617 (1.8%)	5/623 (0.8%)	**OR 0.71** (0.32 to 1.56)	**18 per 1000**	**5 fewer per 1000** (from 12 fewer to 10 more)
Anastomotic leak Osland (CRITICAL OUTCOME)											
1075 (13 studies) 5-24 days	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	undetected	**VERY LOW**[1,5] due to risk of bias, imprecision	17/533 (3.2%)	12/542 (2.2%)	**OR 0.75** (0.39 to 1.45)	**32 per 1000**	**8 fewer per 1000** (from 19 fewer to 14 more)
LOS Hospital Osland (CRITICAL OUTCOME; range of scores: 5.2-24.5; Better indicated by lower values)											
872 (10 studies) 5-24 days	serious[1]	very serious[9,10]	no serious indirectness	serious[5]	undetected	**VERY LOW**[1,5,9,10] due to risk of bias, inconsistency, imprecision	432	440	-	The mean los hospital osland in the control groups was **22.7 days**	The mean los hospital osland in the intervention groups was **1.28 lower** (2.95 lower to 0.38 higher)

[1] None of the studies received a Jadad score (modified) higher than three (range 1-3, median 2) on a scale of 0-5, with higher being better.

[2] The heterogeneity in the studies reported prior to the year 2000 is low (I^2 =16%), while the heterogeneity in the studies reported after 2000 is high (I^2 = 77%) Also, the heterogeneity between the two sub groups (pre 2000 vs. post 2000) is moderate (I^2=52%).

[3] The term "all complications" is not defined. The MA authors only note it is not mortality, nausea and vomiting).

[4] Small number of events and small number of subjects.

[5] Confidence intervals are wide.

[6] The authors included funnel plots. Only the funnel plot for the outcome "Total Complications" suggests publication bias. They go on to state, "the number of studies included in the funnel plots is inadequate to sensitively detect a study bias."

[7] For this outcome, heterogeneity is low. I^2 statistic = 0.

[8] 9 of 15 studies reported no deaths in either group; low number of events. The confidence intervals are very wide.

[9] Uncertain if ICU death shortened LOS for either group.
[10] Heterogeneity for the pre 2000 group is moderate I^2 statistic is 51%, while heterogeneity for the post 2000 group is high 85%.

Arginine vs. Standard for Elective Surgery

There are no forest plots as this is a GRADE of a completed meta analysis.

Question: Should arginine supplemented diets vs standard be used for elective surgical patients?

Bibliography: Drover, J.W., Dhaliwal, R., Weitzel, L., Wischmeyer, P. E., Ochoa, J. B., & Heyland, D. K. (2011). Peri-operataive use of arginine-supplemented diets: A systematic review of the evidence. J. AM Coll Surg, doi doi:10.1016/j.jamcollsurg.2010.10.016

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard	**With Arginine supplemented diets**		**Risk with Standard**	**Risk difference with Arginine supplemented diets** (95% CI)
Infections Drover (CRITICAL OUTCOME; assessed with: number of patients with at least one infection)											
2780 (28 studies) 10-35 days	serious[1]	no serious inconsistency[2,3]	no serious indirectness	serious[4]	undetected[5]	**LOW**[1,2,3,4,5] due to risk of bias, imprecision	346/1248 (27.7%)	253/1532 (16.5%)	**RR 0.59** (0.5 to 0.7)	**277 per 1000**	**114 fewer per 1000** (from 83 fewer to 139 fewer)
Hospital LOS Drover (CRITICAL OUTCOME; range of scores: 4-43; Better indicated by lower values)											
2616 (29 studies) 10-35 days	serious[1]	serious[5,6]	no serious indirectness	no serious imprecision[7]	undetected[4,5]	**LOW**[1,4,5,6,7] due to risk of bias, inconsistency	1226	1390	-	The mean hospital los drover in the control groups was **17 days**	The mean hospital los drover in the intervention groups was **2.38 lower** (3.39 to 1.36 lower)
Mortality Drover (CRITICAL OUTCOME; assessed with: number of patints that died)											

2207 (21 studies) 10-43	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	undetected[5]	**LOW**[1,5,8] due to risk of bias, imprecision	26/982 (2.6%)	32/1225 (2.6%)	**RR 1.08** (0.65 to 1.8)	**26 per 1000**	**2 more per 1000** (from 9 fewer to 21 more)

[1] Over half the studies were not blinded, but it is difficult to blind this type of study. It would be stronger if the outcome assessors had been reported to have been blinded.
[2] The studies pretty much line up to favor the treatment with supplemental arginine in diets. Seven of the 28 studies (one third of total studies) reported a significant decrease in infections. The I2 statistic is 26%, acceptable heterogeneity.
[3] Two of the studies also treated with additional glycine. The authors did a sub analysis with the studies removed and the estimate of effect was similar, and the heterogeneity remained low.
[4] Low number of subjects in many studies included.
[5] The authors of the metaanalysis reported there was no asymmetry noted on the funnel plot.
[6] I2 statisitic is 87%.
[7] Length of stay is difficult to interpret, since it is unknown if early deaths decreased LOS.
[8] Low number of subjects in the included studies, and low number of deaths are reported in many (zero or one death).

Enteral Fish Oil vs Control for Elective Surgery

Question: Should Fish oil vs. control (MCT/LCT) be used for elective surgery? (Including studies from Wei 2005)

Bibliography: De Miranda Torrinhas 2013, Grecu 2003, Han 2012, Heller 2004, Hubner 2012, Jiang 2004, Ma 2012, Kelbel 2002, Makay 2011, Wang 2012, Wichmann 2007

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control (MCT/LCT,	**With Fish oil**		**Risk with Control (MCT/LCT,**	**Risk difference with Fish oil** (95% CI)
Mortality (CRITICAL OUTCOME; assessed with: number of deaths)											
598 (6 studies) 9.9-20 days	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	undetected	**LOW**[1,2,3] due to risk of bias, imprecision	8/296 (2.7%)	10/302 (3.3%)	**RR 1.22** (0.52 to 2.85)	**27 per 1000**	**6 more per 1000** (from 13 fewer to 50 more)
Infectious complications (CRITICAL OUTCOME)											
716 (8 studies) 9.9-20 days	serious[1]	no serious inconsistency[4]	no serious indirectness	serious[2,3,5]	undetected	**LOW**[1,2,3,4,5] due to risk of bias, imprecision	42/361 (11.6%)	26/355 (7.3%)	**RR 0.71** (0.45 to 1.13)	**116 per 1000**	**34 fewer per 1000** (from 64 fewer to 15 more)
LOS Hospital (CRITICAL OUTCOME; Better indicated by lower values)											
388 (5 studies) 9.9-20 days	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias,	193	195	-	The mean LOS Hospital in the control groups was **15.8 days**	The mean LOS Hospital in the intervention groups was **2.56 lower**

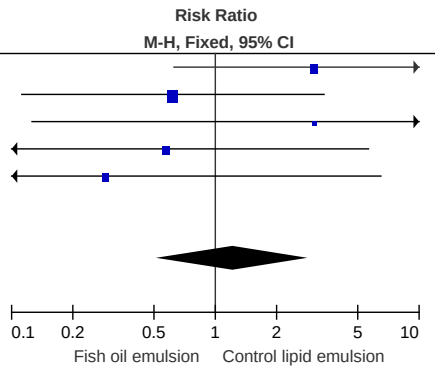
						imprecision				(5.89 lower to 0.77 higher)
LOS ICU (CRITICAL OUTCOME; Better indicated by lower values)										
185 (4 studies) 1.1-4.6 days	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	**LOW**[1,2] due to risk of bias, imprecision	90	95	-	The mean LOS ICU in the control groups was **4.4 days**	The mean LOS ICU in the intervention groups was **1.41 lower** (2.18 to 0.65 lower)

[1] Intention to treat analysis is not common in the included studies.
[2] Small sample sizes
[3] Small number of events
[4] Although the I2 statistic show low heterogeneity, the type of infection included among studies varied greatly. However did not decrease quality for this factor
[5] Most studies were not powered to detect a difference in number of infections

Fish oil vs. control (MCT/LCT mix) lipid emulsion, Outcome: Mortality

	Fish oil emulsion		Control lipid emulsion			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Wichmann 2007	6	127	2	129	21.9%	3.05 [0.63, 14.82]	
Grecu 2003	2	28	3	26	34.3%	0.62 [0.11, 3.41]	
Jiang 2005	1	101	0	103	5.5%	3.06 [0.13, 74.21]	
Kelbel 2002	1	14	2	16	20.6%	0.57 [0.06, 5.65]	2002
Makay 2011	0	14	1	12	17.7%	0.29 [0.01, 6.50]	2011
Han 2012	0	18	0	12		Not estimable	2012
Total (95% CI)		**302**		**298**	**100.0%**	**1.22 [0.52, 2.85]**	
Total events	10		8				

Heterogeneity: Chi² = 3.45, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)

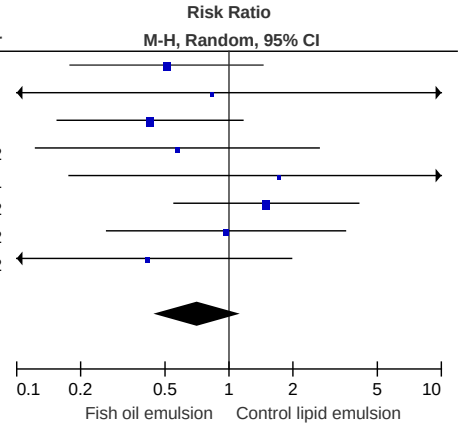


Fish oil vs. control (MCT/LCT mix) lipid emulsion, Outcome: Infectious Complications

	Fish oil emulsion		Control lipid emulsion			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Wichmann 2007	5	127	10	129	19.7%	0.51 [0.18, 1.44]	
Heller 2004	1	24	1	20	2.9%	0.83 [0.06, 12.49]	
Jiang 2005	5	101	12	103	21.2%	0.42 [0.16, 1.16]	
Kelbel 2002	2	14	4	16	9.1%	0.57 [0.12, 2.66]	2002
Makay 2011	2	14	1	12	4.2%	1.71 [0.18, 16.65]	2011
Han 2012	5	12	5	18	21.4%	1.50 [0.55, 4.08]	2012
Wang 2012	4	32	4	31	12.8%	0.97 [0.27, 3.54]	2012
de Miranda Torrinhas 2012	2	31	5	32	8.8%	0.41 [0.09, 1.97]	2012
Total (95% CI)		**355**		**361**	**100.0%**	**0.71 [0.45, 1.13]**	
Total events	26		42				

Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 7 (P = 0.66); I² = 0%

Test for overall effect: Z = 1.45 (P = 0.15)

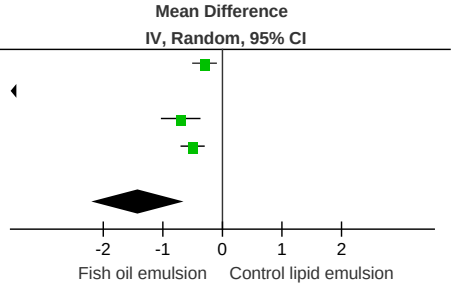


Fish oil vs. control (MCT/LCT mix) lipid emulsion, Outcome: LOS ICU

	Fish oil emulsion			Control lipid emulsion				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Heller 2004	4.3	0.29	24	4.6	0.36	20	28.1%	-0.30 [-0.50, -0.10]	
Grecu 2003	3	1	28	9	3	26	16.6%	-6.00 [-7.21, -4.79]	
Berger 2008	1.6	0.4	12	2.3	0.4	12	27.2%	-0.70 [-1.02, -0.38]	2008
de Miranda Torrinhas 2012	1.1	0.23	31	1.6	0.5	32	28.1%	-0.50 [-0.69, -0.31]	2012
Total (95% CI)			**95**			**90**	**100.0%**	**-1.41 [-2.18, -0.65]**	

Heterogeneity: Tau² = 0.53; Chi² = 84.71, df = 3 (P < 0.00001); I² = 96%

Test for overall effect: Z = 3.63 (P = 0.0003)

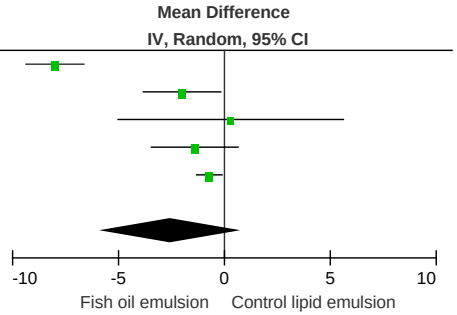


Fish oil vs. control (MCT/LCT mix) lipid emulsion, Outcome: LOS Hospital

	Fish oil emulsion			Control lipid emulsion				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Grecu 2003	12	2	28	20	3	26	21.6%	-8.00 [-9.37, -6.63]	
Jiang 2005	15	5	100	17	8	103	21.0%	-2.00 [-3.83, -0.17]	
Heller 2004	19.1	9.6	24	18.8	8.4	20	14.3%	0.30 [-5.02, 5.62]	
Berger 2008	9.9	2.4	12	11.3	2.7	12	20.7%	-1.40 [-3.44, 0.64]	2008
de Miranda Torrinhas 2012	11.29	1.14	31	12	1.29	32	22.3%	-0.71 [-1.31, -0.11]	2012
Total (95% CI)			**195**			**193**	**100.0%**	**-2.56 [-5.89, 0.77]**	

Heterogeneity: Tau² = 12.84; Chi² = 92.02, df = 4 (P < 0.00001); I² = 96%

Test for overall effect: Z = 1.51 (P = 0.13)



Immunonutrition vs Standard EN in Postoperative Patients

There are **no forest plots** as this is a GRADE of a completed meta-analysis.

Question: Should two or more immuno-nutrition components vs. iso-caloric, isonitrogenous STD EN be used for post-operative outcomes in subjects undergoing elective major open gastrointestinal surgery?

Bibliography: Marimuthu, K., Varadhan, K. K., Ljungqvist, O., & Lobo D. (2012). A meta-analysis of hte effect of combinations of immune modulation nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg, 255, 1060-1068.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Iso-caloric, isonitrogenous STD EN	**With Two or more immuno-nutrition components**		**Risk with Iso-caloric, isonitrogenous STD EN**	**Risk difference with Two or more immuno-nutrition components** (95% CI)
Post op infectious complications (CRITICAL OUTCOME)											
2496 (26 studies) 9-31 days	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	undetected	**MODERATE**[1,2] due to risk of bias	336/1244 (27%)	215/1252 (17.2%)	**RR 0.64** (0.55 to 0.74)	**270 per 1000**	**97 fewer per 1000** (from 70 fewer to 122 fewer)
Non-infectious complications (CRITICAL OUTCOME)											
1941 (20 studies) 9-31 days	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	reporting bias strongly suspected[4]	**LOW**[1,3,4] due to risk of bias, publication bias	257/968 (26.5%)	210/973 (21.6%)	**RR 0.82** (0.71 to 0.95)	**265 per 1000**	**48 fewer per 1000** (from 13 fewer to 77 fewer)
LOS Hospital (CRITICAL OUTCOME; range of scores: 9-19; Better indicated by lower values)											
2097 (20 studies)	serious[1]	serious[5]	no serious indirectness	no serious imprecision	undetected	**LOW**[1,5] due to risk of bias,	1045	1052	**-**	The mean los hospital in the control groups	The mean los hospital in the intervention

9-31 days						inconsistency			was **17.4 days**	groups was **1.88 lower** (2.91 to 0.84 lower)
Post-operative mortality (CRITICAL OUTCOME)										
2380 (25 studies) 9-31 days	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	undetected	**LOW**[6] due to risk of bias, imprecision	29/1189 (2.4%)	22/1191 (1.8%)	**RR 0.83** (0.49 to 1.41)	**24 per 1000**	**4 fewer per 1000** (from 12 fewer to 10 more)