

Early enteral nutrition in critical illness: How early is early?

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Summary of this talk

- Provide a context for this talk.
- Review the most recent clinical recommendations on early EN.
- Compare evidence supporting the 2015 Canadian nutrition guideline to the 2016 ASPEN guideline.
- Conclude.



Background: Review of the Guidelines

- The concept of 'early' enteral feeding was popularised in the mid '80s.

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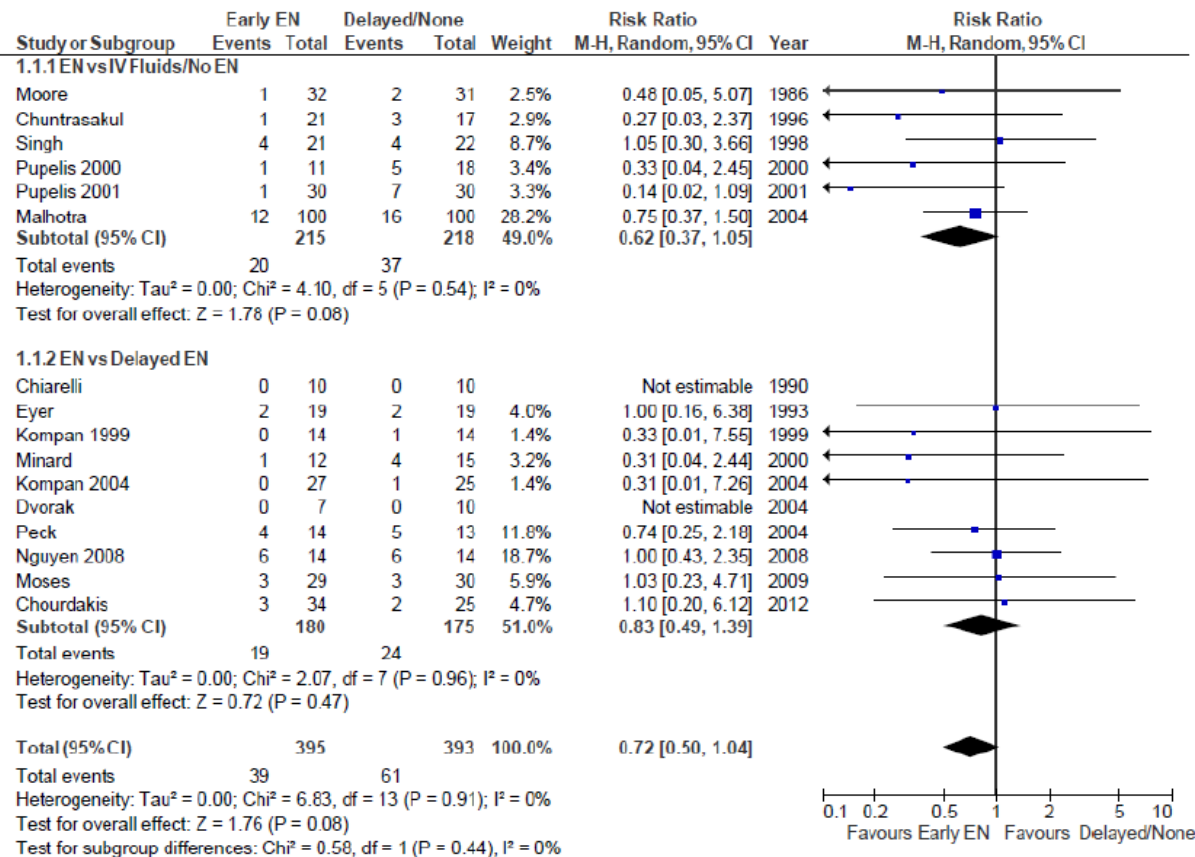
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2015 Canadian guideline

< 48 h – Canadian guideline

Figure 1. Studies comparing early EN vs delayed nutrient intake: Mortality

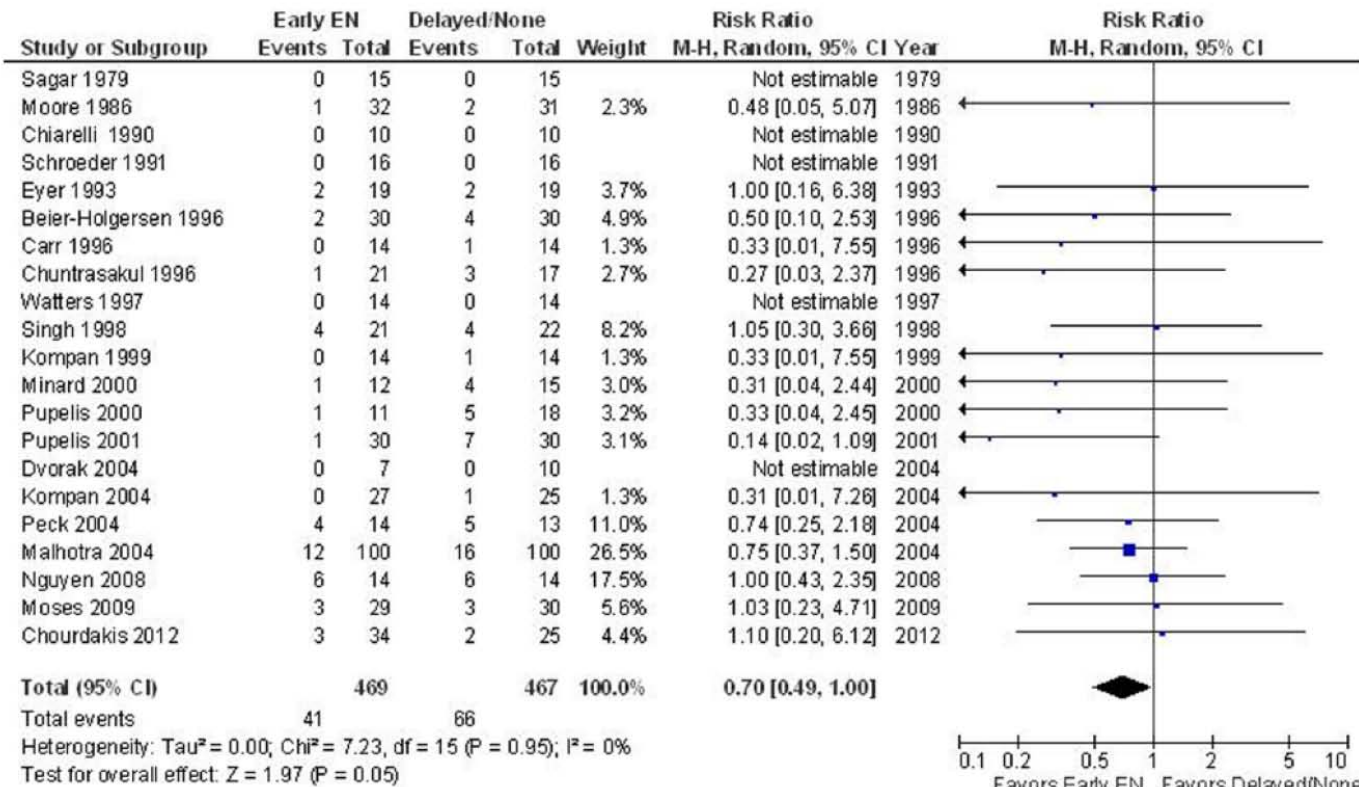


- 16 clinical trials
- $p=0.08$ (trend)
- mortality reduction by 6%



2016 ASPEN guideline

< 48 h – 2016 ASPEN



- 21 clinical trials
- p=0.05 (significant)
- mortality reduction by 5%

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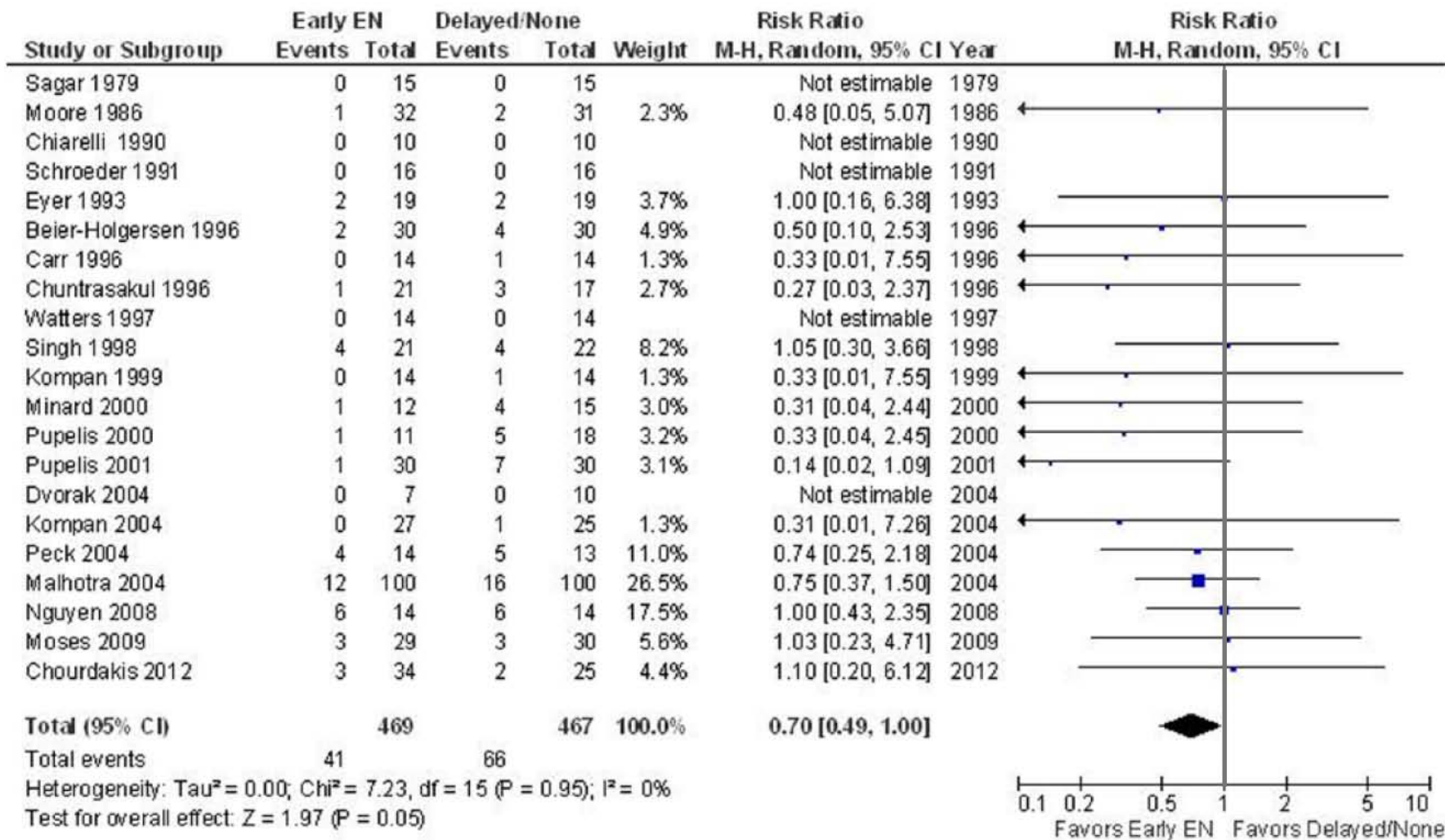


2015 Canadian vs. 2016 ASPEN guideline

- We need to understand why the 2016 ASPEN guideline has **5 more clinical trials** than the 2015 Canadian guideline.

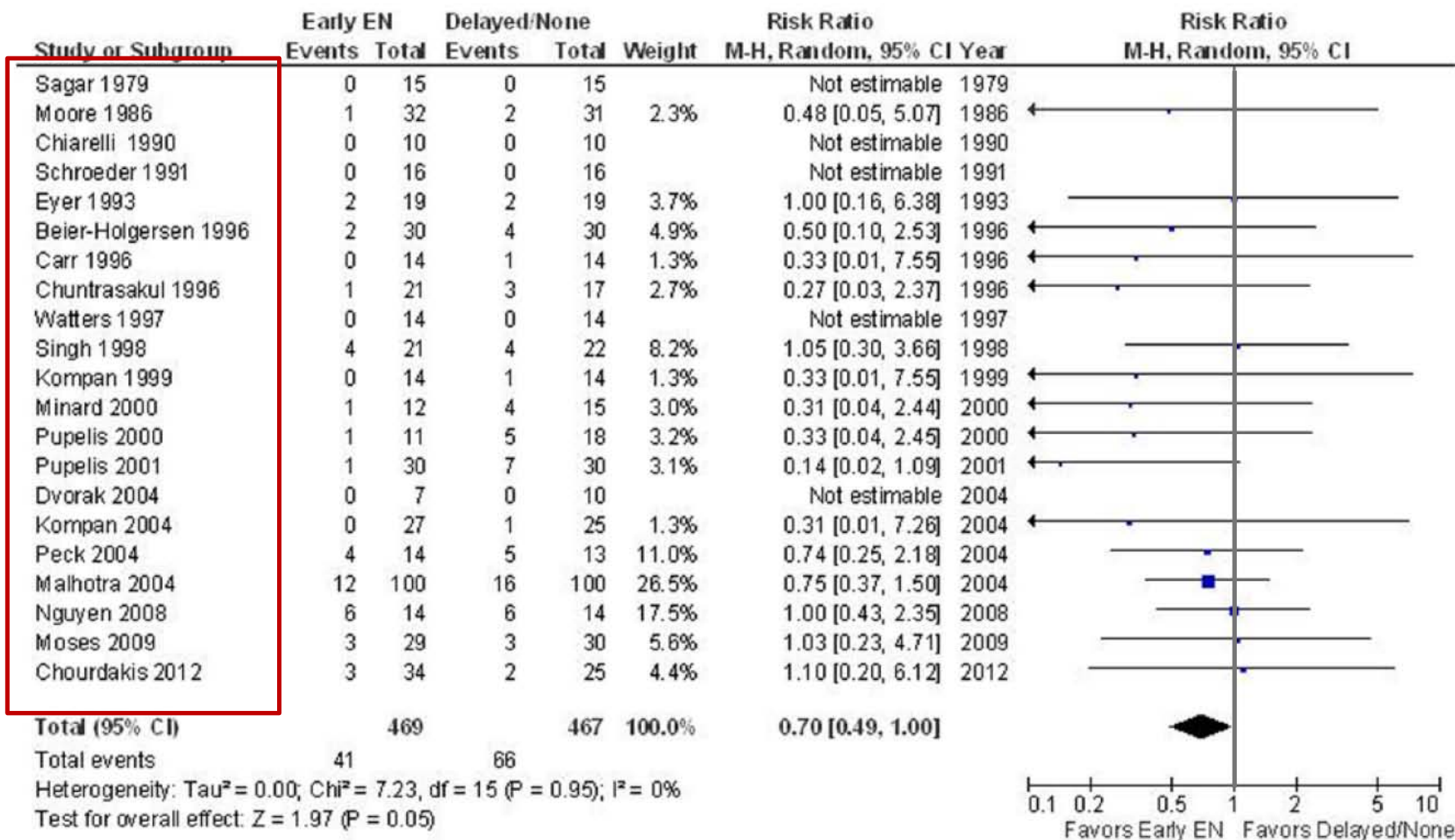


2016 ASPEN guideline



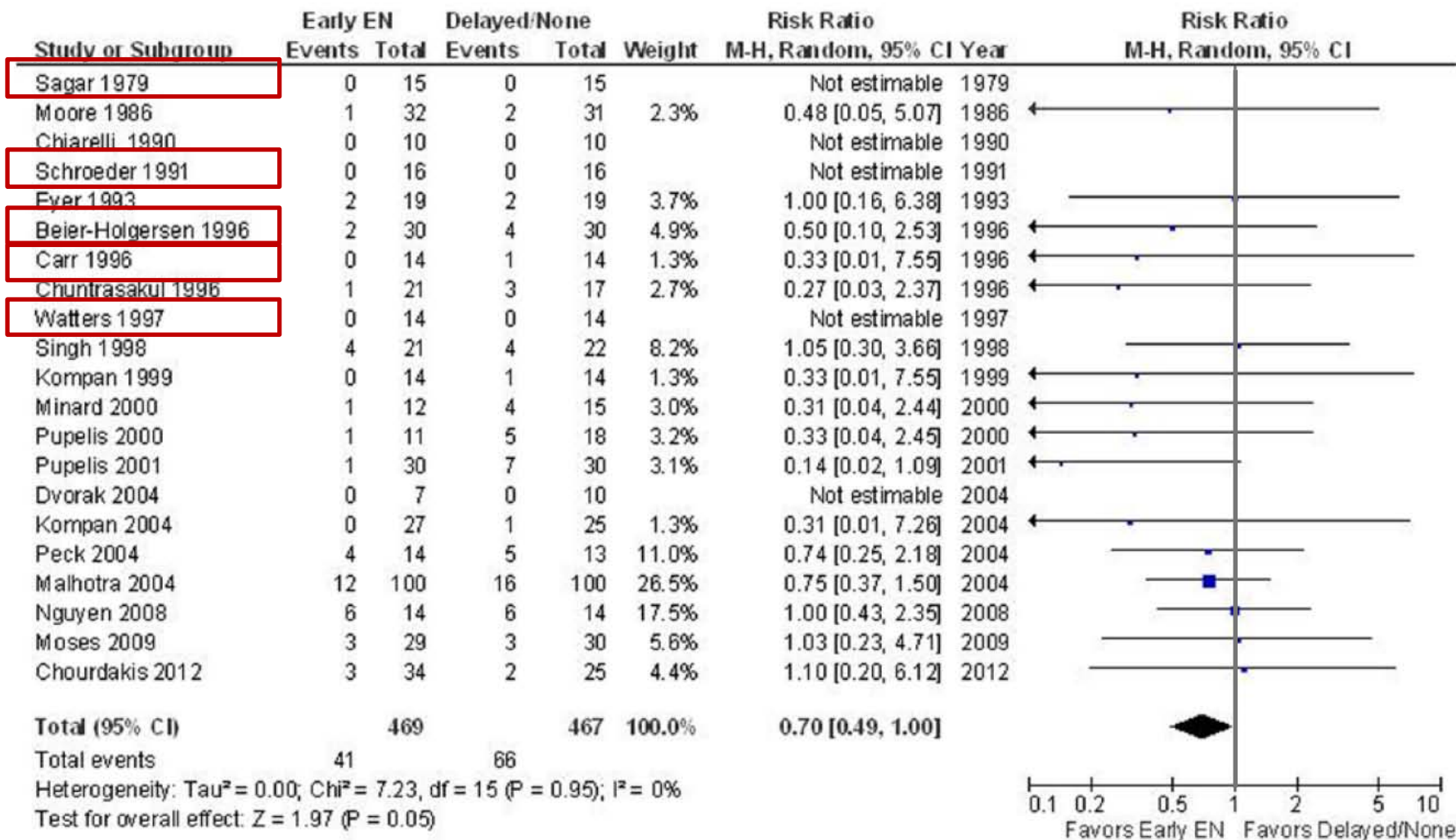


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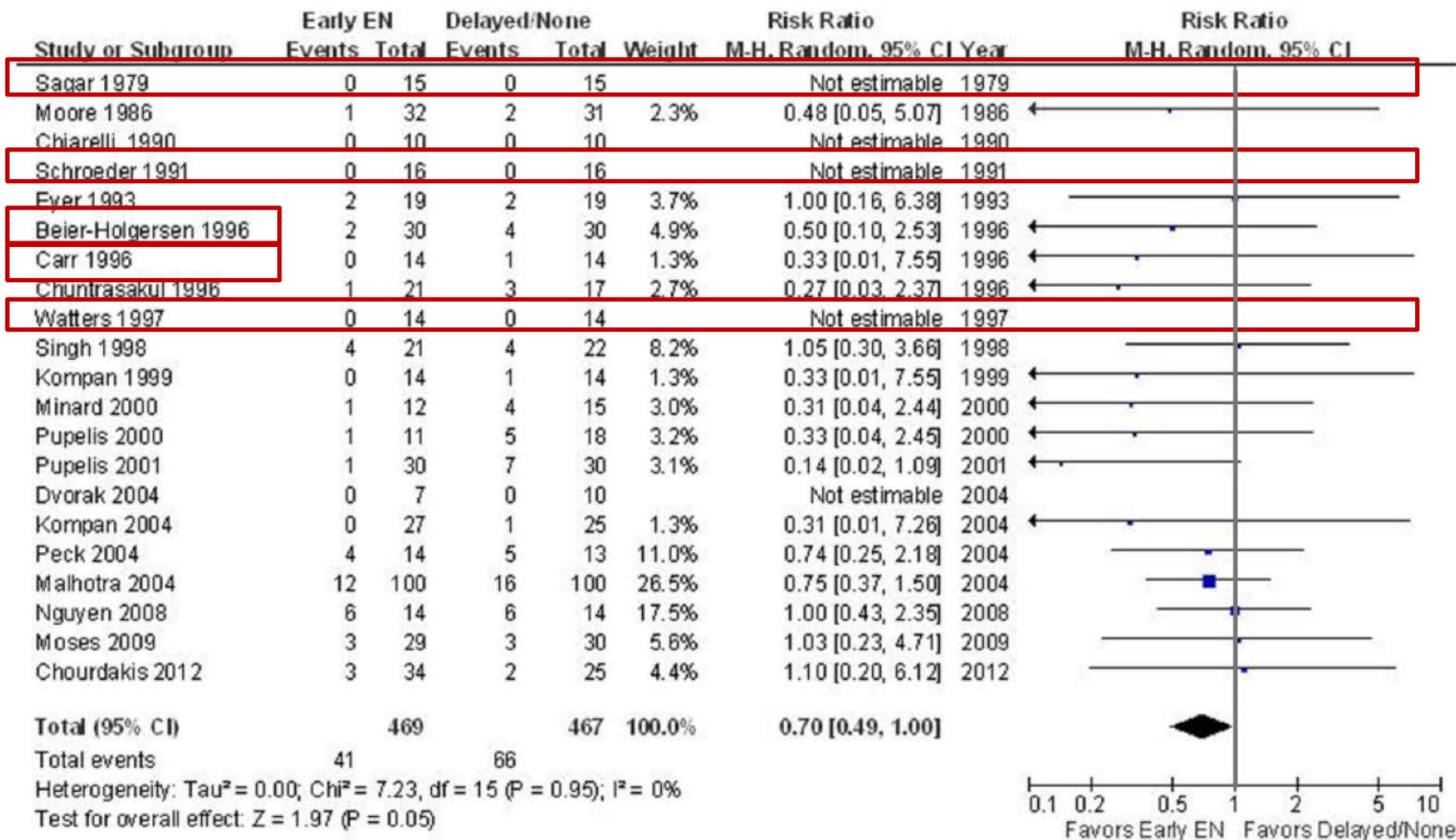


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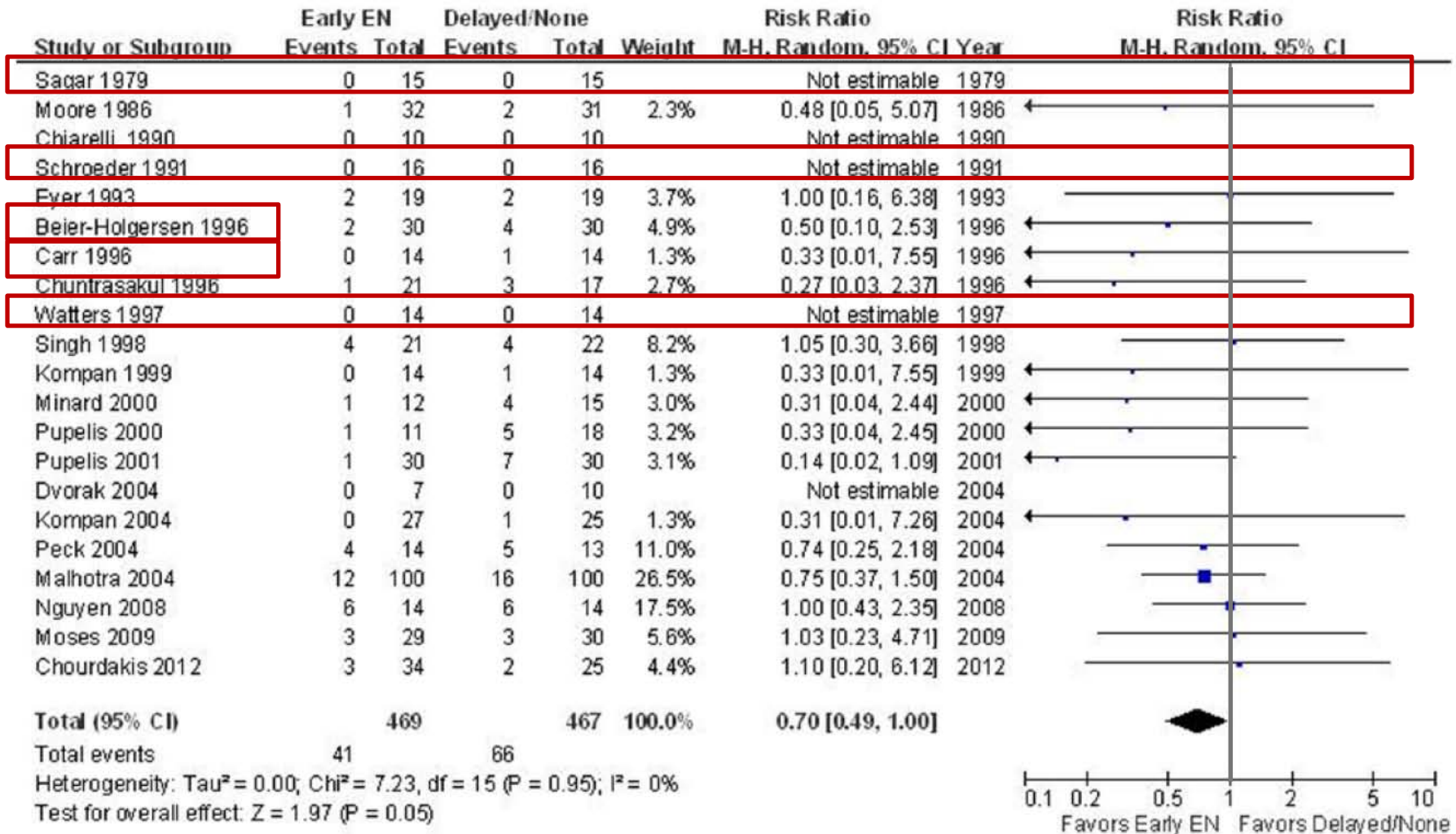


2015 Canadian vs. 2016 ASPEN guideline

- Sagar 1979, Schroeder 1991 and Walters 1997 **have zero deaths**.
 - Could not influence the difference in results (p-value) between the 2015 Canadian and 2016 ASPEN guidelines.



2015 Canadian vs. 2016 ASPEN guideline

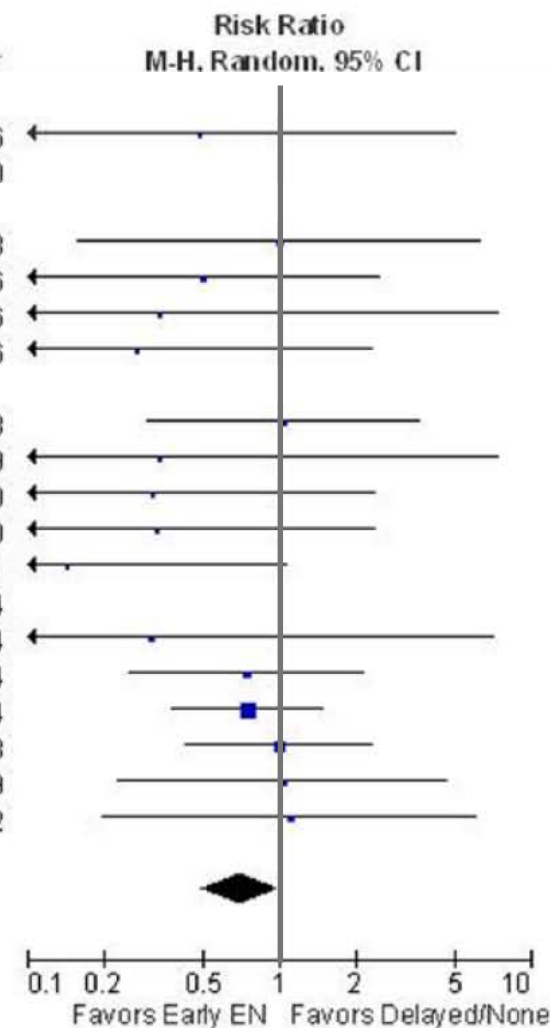




2015 Canadian vs. 2016 ASPEN guideline

Study or Subgroup	Early EN		Delayed/None		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]	1986	
Chiarelli 1990	0	10	0	10		Not estimable	1990	
Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]	1993	
Beier-Holgersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]	1996	
Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1996	
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Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]	2000	
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Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]	2004	
Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]	2008	
Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]	2009	
Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]	2012	
Total (95% CI)		469		467	100.0%	0.70 [0.49, 1.00]		

Total events: Early EN 41, Delayed/None 66
 Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.23$, $df = 15$ ($P = 0.95$); $I^2 = 0\%$
 Test for overall effect: $Z = 1.97$ ($P = 0.05$)





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- Beier-Holgersen 1996

Gut 1996; 39: 833-835

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Influence of postoperative enteral nutrition on postsurgical infections

R Beier-Holgersen, S Boesby

Abstract

Background—This study was undertaken to test the hypothesis that early enteral nutrition might reduce the incidence of serious complications after major abdominal surgery.

Methods—In a randomised double blind prospective trial 30 patients received Nutri-drink and 30 patients received placebo through a nasoduodenal feeding tube. On the day of operation the patients were given median 600 ml of either nutrition or

incidence of septic complications. Elemental diet infusion began 12 to 18 hours post-operatively.² In a meta-analysis of the effect of enteral versus parenteral nutrition in high risk surgical patients the authors found that patients receiving enteral nutrition had a lower incidence of septic complications.³ None of these investigations were placebo controlled and therefore not blinded. In 1994 Consensus in Clinical Nutrition⁴ still concluded that, after major surgery, in a well nourished patient, nutritional support should only be considered



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Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection

Cornelia S Carr, K D Eddie Ling, Paul Boulos, Mervyn Singer

Abstract

Objectives—To assess whether immediate postoperative enteral feeding in patients who have undergone gastrointestinal resection is safe and effective.

Design—Randomised trial of immediate postoperative enteral feeding through a nasojejunal tube v conventional postoperative intravenous fluids until the reintroduction of normal diet.

Setting—Teaching hospitals in London.

Subjects—30 patients under the care of the participating consultant surgeon who were undergoing elective laparotomies with a view to gastrointestinal resection for quiescent, chronic gastrointestinal disease. Two patients did not proceed to resection.

healing in an enterally fed group after bowel resection but calculated that dietary requirements were not fulfilled until the introduction of normal diet.¹¹

We undertook a pilot study in patients undergoing bowel resection by comparing conventional management with immediate enteral feeding in which protein calorie requirements were met within 8 to 12 hours postoperatively. Assessment was made of safety, nutritional state, clinical outcome, and effects on gut mucosal permeability.

Subjects and methods

Patients undergoing intestinal resection were con-



2015 Canadian vs. 2016 ASPEN guideline

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- Beier-Holgersen 1996, Carr 1996
 - Neither study reports any patients requiring care in the ICU, post-op mechanical ventilation or any other interventions requiring ICU admission.



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J Gastrointest Surg (2009) 13:569–575

DOI 10.1007/s11605-008-0592-x

REVIEW ARTICLE

Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic review and Meta-analysis

Stephen J. Lewis • Henning K. Andersen • Steve Thomas



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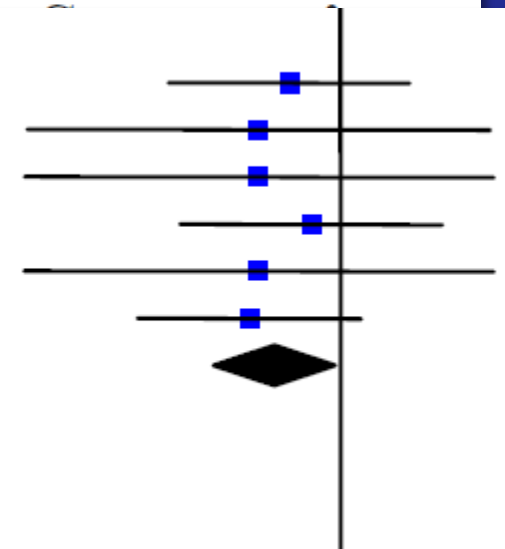
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Hartsell 1997	0/29	1/29
Heslin 1997	2/97	3/98
Stewart 1998	0/40	1/40
Mulrooney 2004	2/36	7/37
Subtotal (95% CI)	246	248

Total events: 6 (Treatment), 17 (Control)

Test for heterogeneity: $\text{Chi}^2 = 0.60$, $\text{df} = 5$ ($P = 0.99$), $I^2 = 0\%$, $p = 0.988$

Test for overall effect: $Z = 2.13$ ($P = 0.03$)





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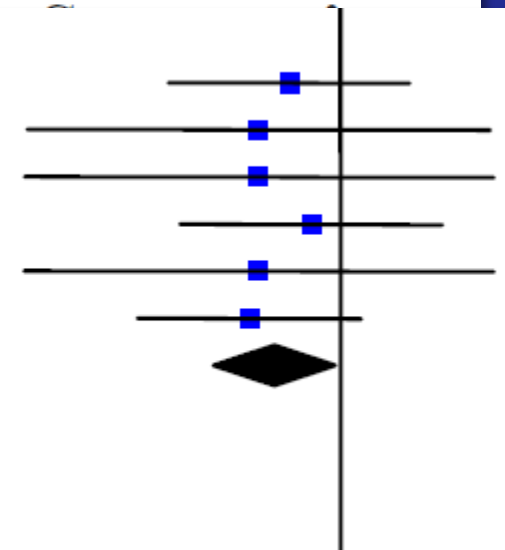
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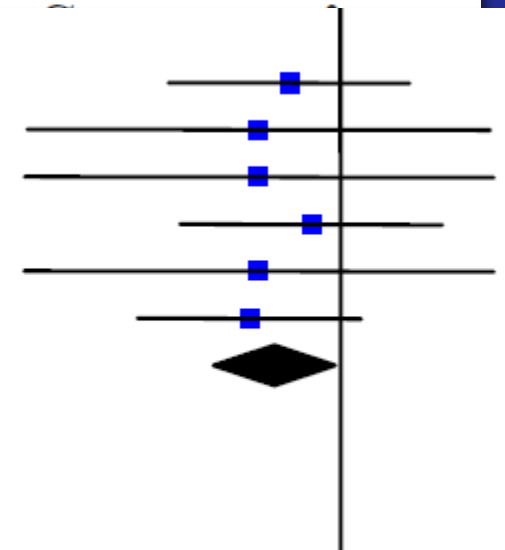
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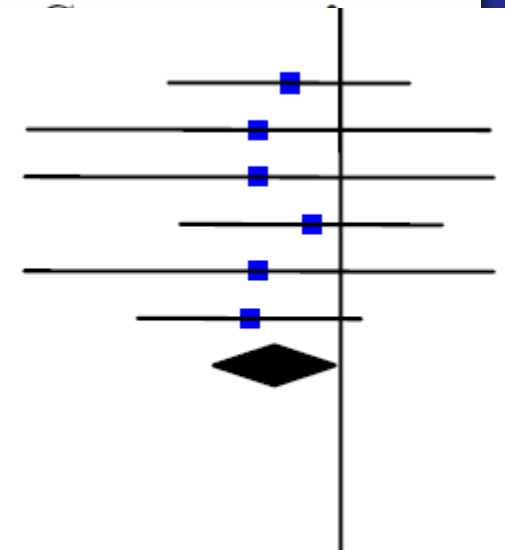
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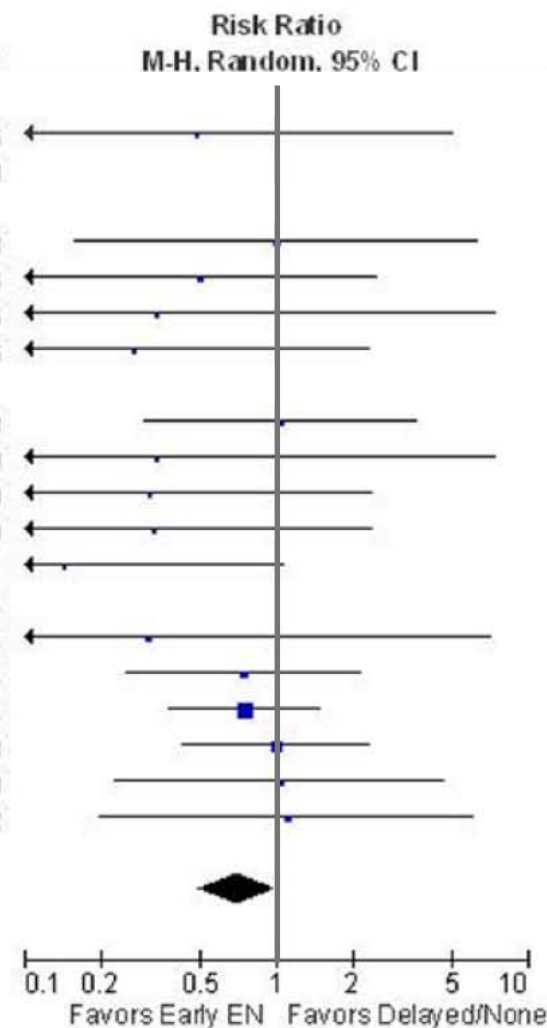
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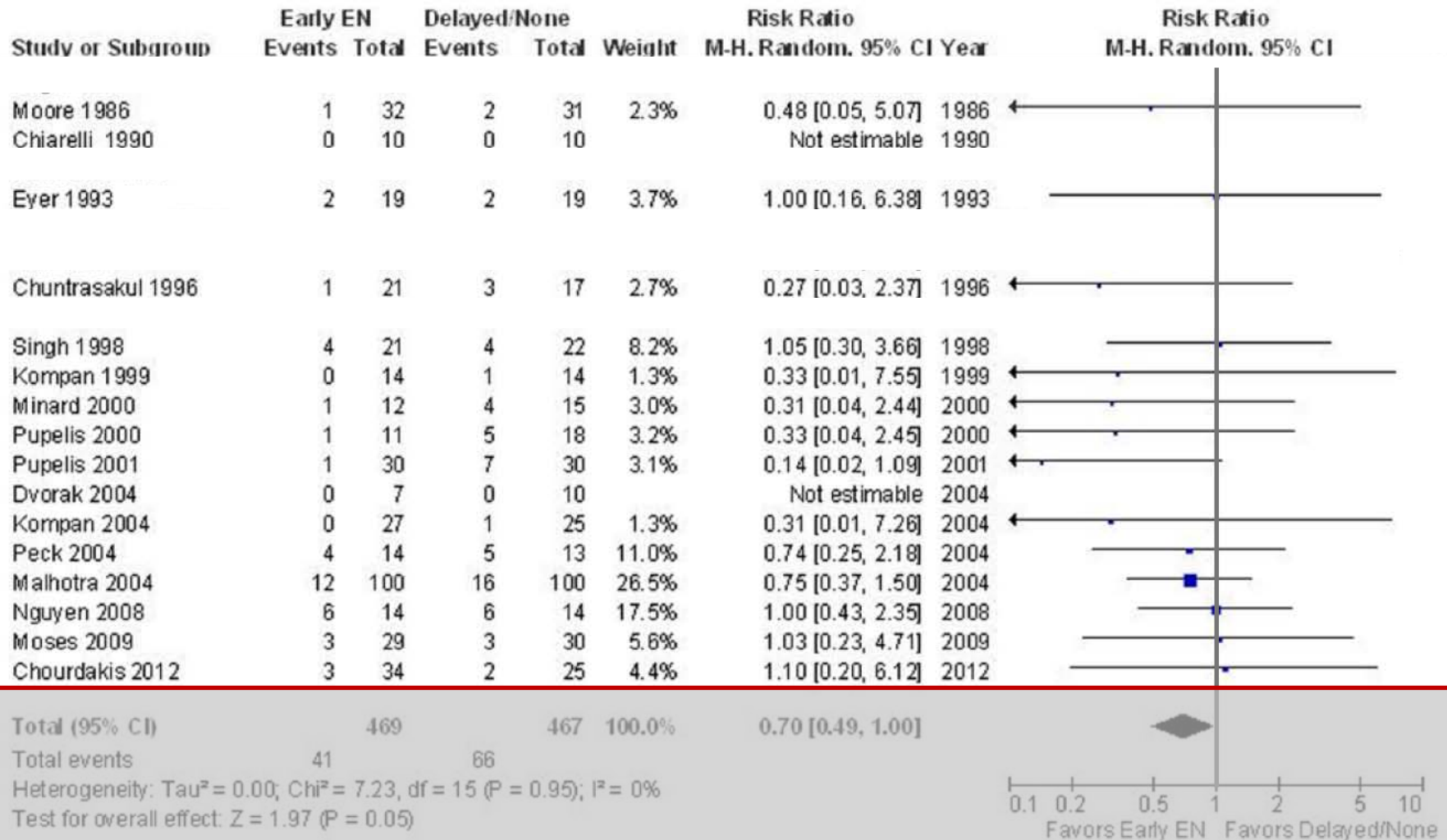
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Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]	2000	
Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]	2000	
Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]	2001	
Dvorak 2004	0	7	0	10		Not estimable	2004	
Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]	2004	
Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]	2004	
Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]	2004	
Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]	2008	
Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]	2009	
Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]	2012	
Total (95% CI)		469		467	100.0%	0.70 [0.49, 1.00]		

Total events 41 66
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.23$, $df = 15$ ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: $Z = 1.97$ ($P = 0.05$)

0.1 0.2 0.5 1 2 5 10
Favors Early EN Favors Delayed/None

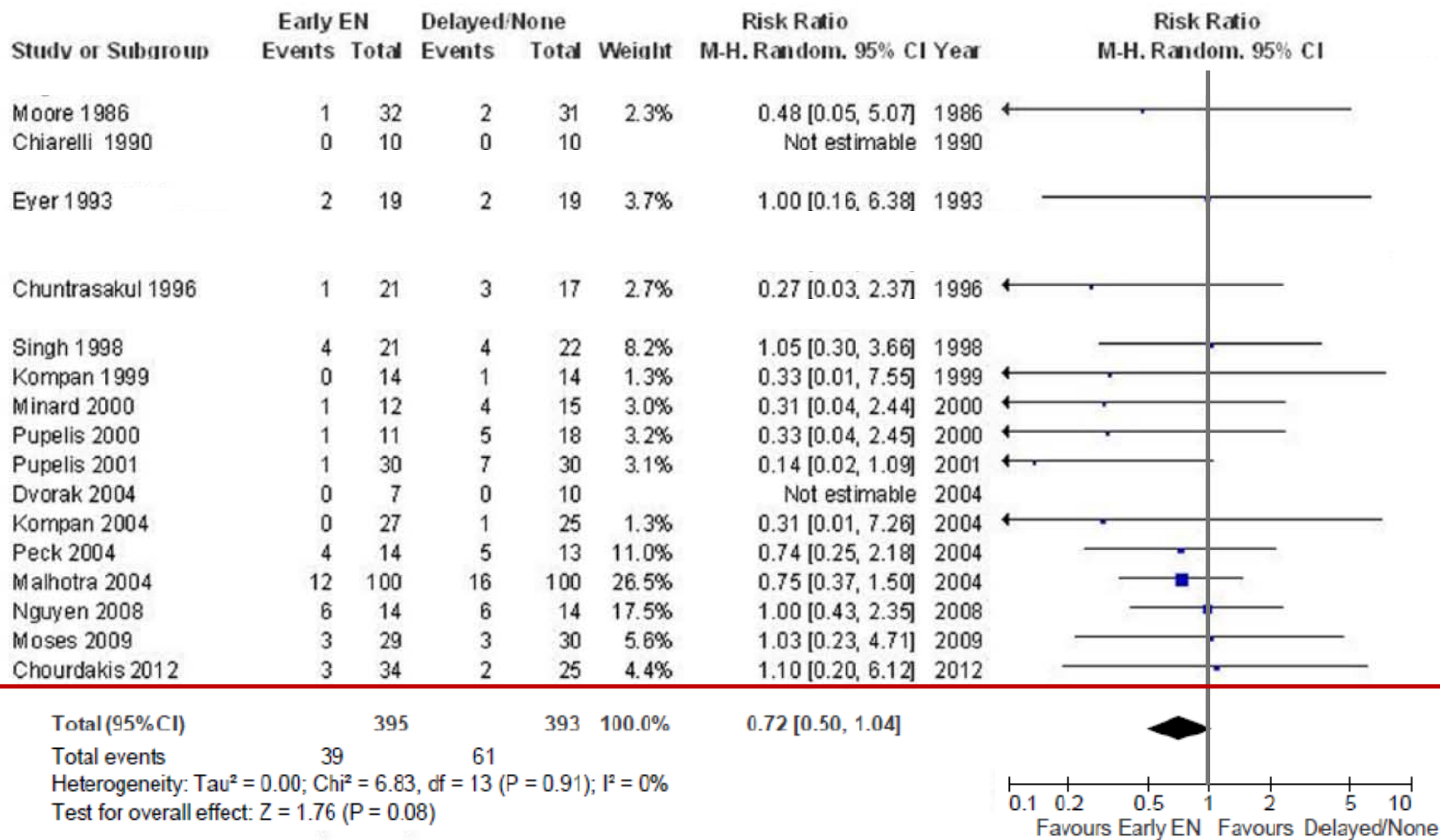


2015 Canadian vs. 2016 ASPEN guideline





2015 Canadian vs. 2016 ASPEN guideline





2015 Canadian vs. 2016 ASPEN guideline

- Sagar 1979, Schroeder 1991 and Walters 1997 have zero deaths.
 - Could not influence the difference in results between the 2015 Canadian and 2016 ASPEN guideline results.
- Beier-Holgersen 1996, Carr 1996
 - Neither study reports any patients requiring care in the ICU, post-op mechanical ventilation or any other interventions requiring ICU admission.
 - *These are elective surgery patients!*
- *With the removal of these five studies (Sagar 1979, Schroeder 1991, Walters 1997, Beier-Holgersen 1996, Carr 1996) the 2016 ASPEN guideline and the 2015 Canadian guideline are in complete agreement: There is a trend ($p=0.08$) towards a reduction in mortality if EN is started within 48 h of ICU admission.*



Background: Review of the Guidelines

- The concept of 'early' enteral feeding was popularised in the mid '80s.
- Five major clinical practice guidelines recommend *early* EN.

< 48 h – Canadian guideline,	Evidence of trend.
< 24 h – ACCEPT guideline (also Canadian),	Significant evidence.
< 24 h – Australian and New Zealand guideline,	Significant evidence.
< 24 h – European (ESPEN) guideline and	Significant evidence.
< 48 h – American (ASPEN and SCCM) guideline	Evidence of trend.

Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma—a prospective, randomized study. *J Trauma* 1986;26:874–881

Heyland DK, *et al.* The 2015 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Martin CM, Doig GS, Heyland DK, Morrison T and Sibbald WJ. Multicentre, cluster randomized clinical trial of algorithms for critical care enteral and parenteral therapy (ACCEPT). *CMAJ* 2004;170(2):197-204.

Doig GS and Simpson F. Evidence-based guidelines for nutritional support of the critically ill: Results of a bi-national guidelines development conference. First Edition, EvidenceBased.net, Sydney, Australia, 2005.

Kreymann KG, Berger MM, Deutz NE, *et al.* ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clinical Nutrition* 2006;25: 210–223.

McClave SA, Taylor BE, Martindale RG, *et al.* Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *J Parenter Enteral Nutr* 2016;40(2):159-211.



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Evidence for early EN in critical illness

Intensive Care Med (2009) 35:2018–2027
DOI 10.1007/s00134-009-1664-4

SYSTEMATIC REVIEW

Gordon S. Doig
Philippa T. Heighes
Fiona Simpson
Elizabeth A. Sweetman
Andrew R. Davies

Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* 2009 Dec;35(Issue 12):2018-2027.



Meta-analysis of early EN in critical illness

Comprehensive Literature search

- MEDLINE (<http://www.PubMed.org>) and EMBASE (<http://www.EMBASE.com>)
- Academic and industry experts were contacted,
- Reference lists of identified systematic reviews and evidence-based guidelines were hand searched by at least two authors.
- The search was not restricted by Language.

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* **2009** Dec;35(Issue 12):2018-2027.



Meta-analysis of early EN in critical illness

Chiarelli, 1990: 20 pts, burns

Kompan, 1999: 36 pts, trauma

Kompan, 2004: 52 pts, trauma

Nguyen, 2008: 28 pts, med/surg critically ill

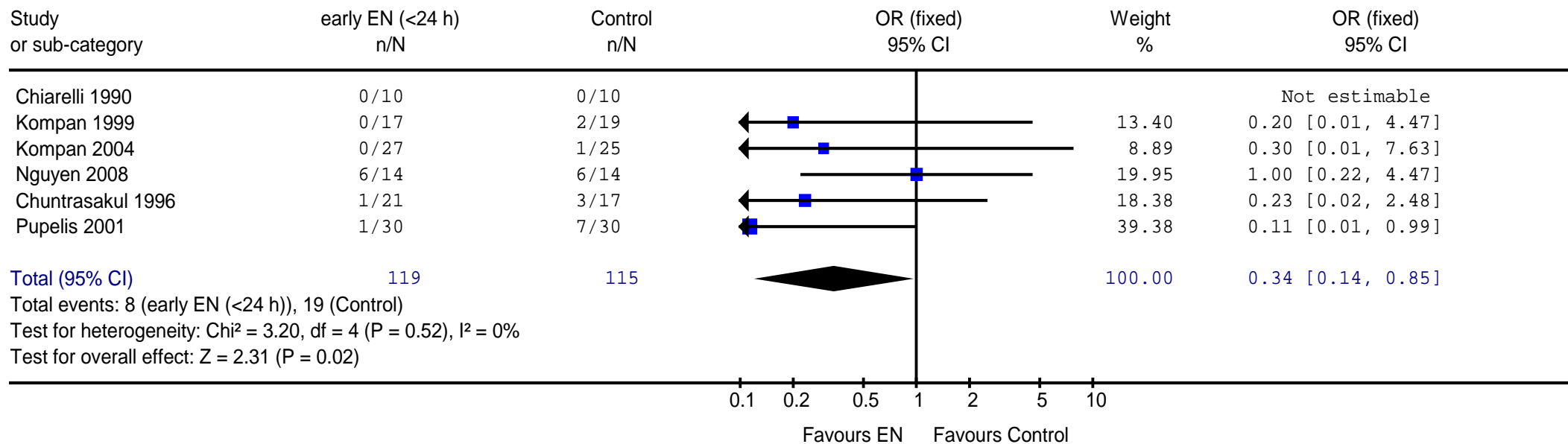
Chuntrasakul, 1996: 38 pts, trauma

Pupelis, 2001: 60 pts, severe pancreatitis and peritonitis



Results: Primary MA, mortality

Review: Early EN (<24h) vs Control (Primary Analysis)
 Comparison: 01 early EN vs Control
 Outcome: 01 Mortality, Intention to treat analysis



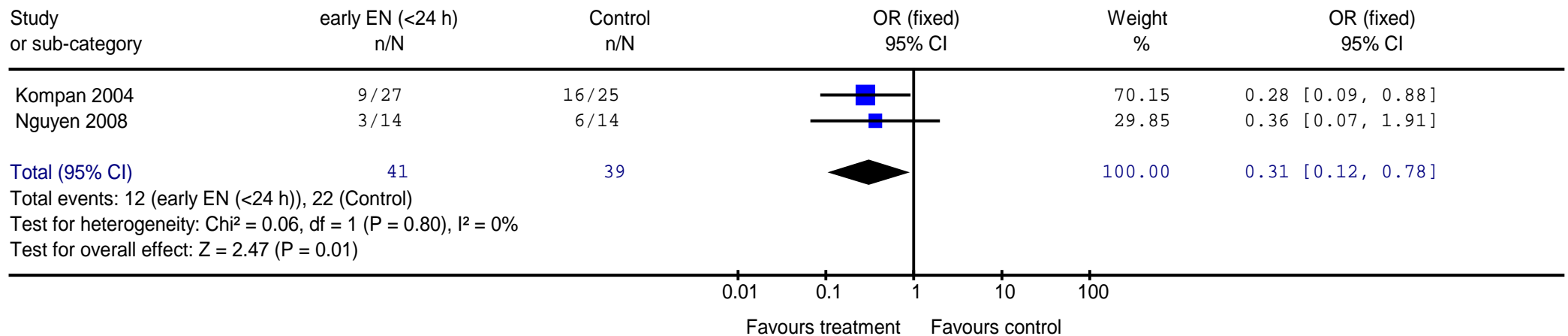
Significant reduction in mortality (**10% absolute reduction, P=0.02**)

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* 2009 Dec;35(Issue 12):2018-2027.



Results: Primary MA, Pneumonia

Review: Early EN (<24h) vs Control (Primary Analysis)
 Comparison: 01 early EN vs Control
 Outcome: 02 Pneumonia, Intention to treat analysis



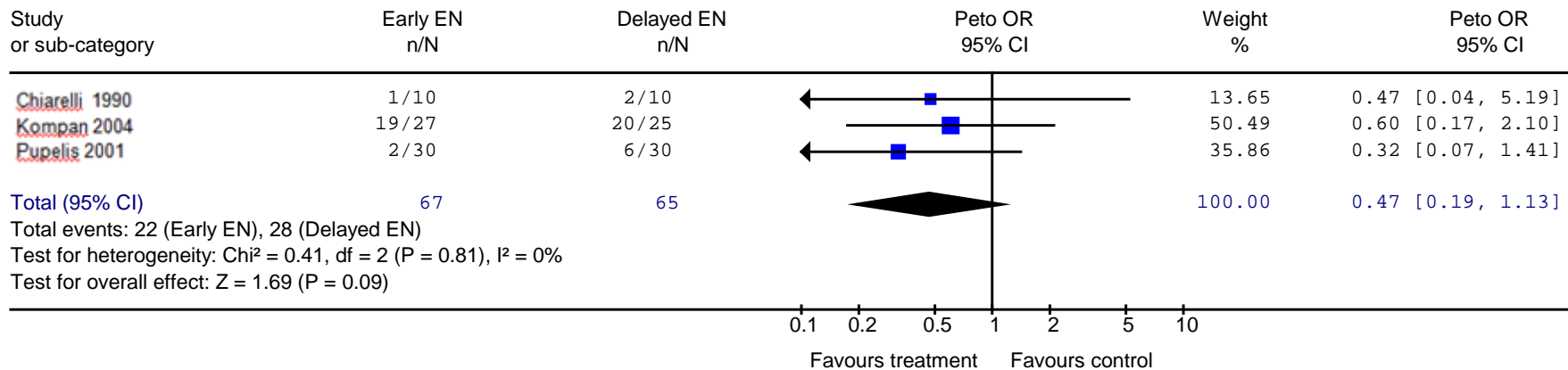
Significant reduction in pneumonia (**27% absolute reduction, P=0.01**)

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* 2009 Dec;35(Issue 12):2018-2027.



Gut dysfunction

Review: Early EN (<24h) vs Standard Care
 Comparison: 01 early EN vs Standard Care
 Outcome: 03 Complications (Gut Dysfunction)



Trend towards a reduction in gut dysfunction (10% absolute reduction, $p=0.09$)
 One included trial demonstrated a significantly shorter duration of gut dysfunction ($p=0.045$)



ICU length of stay

Doig et al

Dovepress

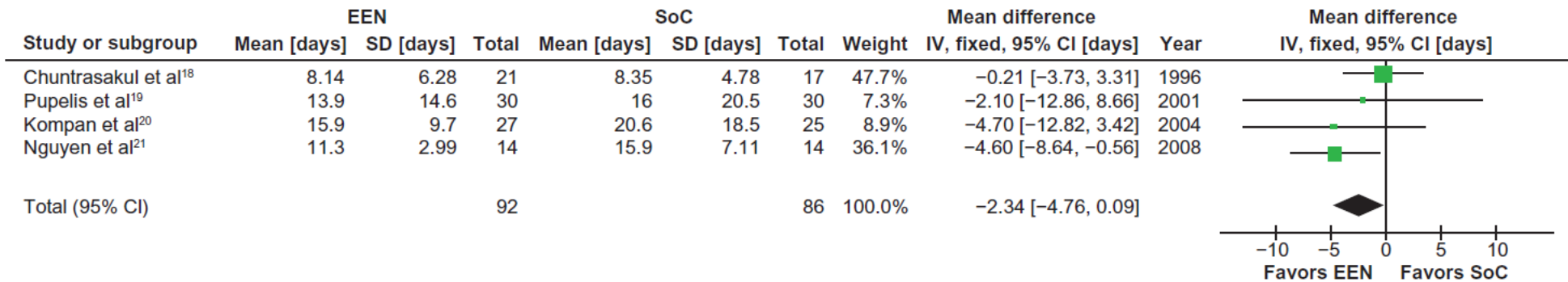


Figure 1 Meta-analysis of ICU length of stay: early enteral nutrition vs standard care.

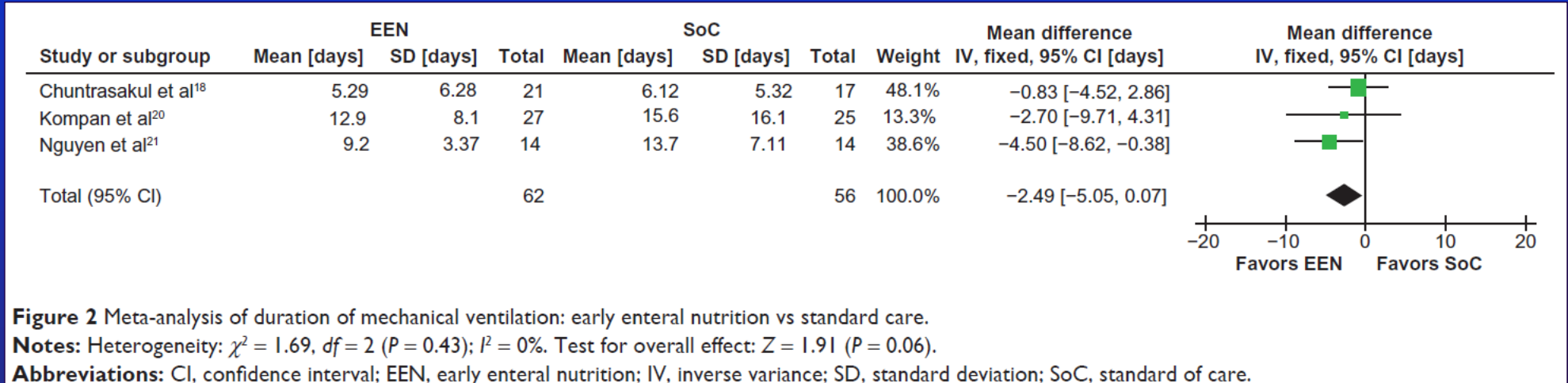
Notes: Heterogeneity: $\chi^2 = 2.94$, $df = 3$ ($P = 0.40$); $I^2 = 0\%$. Test for overall effect: $Z = 1.87$ ($P = 0.06$).

Abbreviations: CI, confidence interval; EEN, early enteral nutrition; ICU, Intensive Care Unit; IV, inverse variance; SD, standard deviation; SoC, standard of care.

Trend towards reduced length of ICU stay with early EN (2.34 days, $P = 0.06$)



Duration of MV



Trend towards reduced mechanical ventilation with early EN (2.49 days, $P = 0.06$)



Early EN in Upper GI Sx: Indirect evidence



Early EN in Upper GI Sx: Indirect evidence

- A Meta-analysis comparing RCT's of early feeding (within 24h) versus no feeding in patients undergoing gastrointestinal surgery.
- 13 studies, 1,173 patients

Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of Intestinal Surgery versus later commencement of feeding: A systematic review and Meta-analysis. *J Gastrointest Surg* 2009;13:569-575.



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- Early feeding was **not** associated with **any harms**:
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 - Anastomotic dehiscence (2.8% eEN vs 4.3%, $p=0.27$)
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“There is no obvious benefit for keeping patients “nil by mouth” after gastrointestinal surgery”



Summary



Summary

Meta-analysis of all available trials demonstrate a **significant** reduction in mortality if EN is provided **within 24 h of ICU admission**.

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Meta-analysis of all available trials demonstrate a **trend** towards a reduction in mortality if EN is provided **within 48h of ICU admission**.



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Meta-analysis of all available trials demonstrate a **trend** towards a reduction in mortality if EN is provided **within 48h of ICU admission**.

There is no evidence of any mortality benefit if EN is commenced later than 48 h after ICU admission.



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Meta-analysis of all available trials demonstrate a **significant** reduction in mortality if EN is provided **within 24 h of ICU admission**.

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Indirect evidence from elective GI surgery patients demonstrates a **significant** reduction in mortality if EN is **commenced on the same day as surgery (< 24 h)**.



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There is no evidence of any mortality benefit if EN is commenced later than 48 h after ICU admission.

Indirect evidence from elective GI surgery patients demonstrates a **significant** reduction in mortality if EN is **commenced on the same day as surgery (< 24 h)**.

Pneumonia, gut dysfunction, duration of mechanical ventilation and ICU stay may also be reduced if EN is commenced **within 24 h of ICU admission**.



How was early (< 24 h) EN initiation achieved?

Study	Patient population	Early EN intervention
Chiarelli 1990	Thermal injury (25% to 60% TBSA). No inhalational injury. Mean survival probability 0.73±0.10.	Immediately after admission: 50 ml/h 'homemade' EN (1900kcal/L and 79 g protein/L) via NGT increasing over 3-4 days. Goals set with Curreri formula . Rate did not exceed 150 ml/h.
Chuntrasakul 1996	Trauma (ISS > 20 and < 40). Mean ISS 29±1.5	Immediately after resuscitation or surgery: 30 mls/h $\frac{3}{4}$ -strength EN (Traumacal™) via NGT, concentration increased over time. Goals estimated using modified Harris-Benedict equation. TPN was added if goals were not met.
Kompan 1999	Trauma (ISS > 25) Mean ISS 33.6±10 Mean APACHE II 11.5±5.8	Immediately after resuscitation: EN (Jevity™) started at 20 ml/h via NGT. Increased to 50% of estimated goal on Day 1, 75% of estimated goal on Day 2 and 100% of goal on Day 3. Estimated goal was set at 25-35 nonprotein kcal/kg per day and 0.2 – 0.3 g nitrogen / kg per day at 72 hours post ICU admission. TPN was added to meet estimated requirements.
Pupelis 2001	Severe pancreatitis and peritonitis Mean APACHE II 11.5±5.4	Within 12 h of surgery: EN (Nutrison Standard™ or Nutrison Pepti™) via NJT started at 20-25ml/h. Increase based in individual tolerance to 1 L per day by Day 3 post-op. Patients also received an average of 500kcal/day from IV dextrose.
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Nguyen 2008	Mechanically ventilated ICU patients APACHE II 22.4±1.2	Within 24 h of admission: EN via NGT at 40 ml/h and increased by 20ml/h q6h to goal, if tolerated (aspirates <250mls). Goal was determined by a dietitian , based on patient's BMI.



How was early (< 24 h) EN initiation achieved?

Study	Patient population	Early EN intervention
Chiarelli 1990	Thermal injury (25% to 60% TBSA). No inhalational injury. Mean survival probability 0.73±0.10.	Immediately after admission: 50 ml/h 'homemade' EN (1900kcal/L and 79 g protein/L) via NGT increasing over 3-4 days. Goals set with Curreri formula . Rate did not exceed 150 ml/h.
Chuntrasakul 1996	Trauma (ISS > 20 and < 40). Mean ISS 29±1.5	Immediately after resuscitation or surgery: 30 mls/h ¾-strength EN (Traumacal™) via NGT, concentration increased over time. Goals estimated using modified Harris-Benedict equation. TPN was added if goals were not met.
Kompan 1999	Trauma (ISS > 25) Mean ISS 33.6±10 Mean APACHE II 11.5±5.8	Immediately after resuscitation: EN (Jevity™) started at 20 ml/h via NGT. Increased to 50% of estimated goal on Day 1, 75% of estimated goal on Day 2 and 100% of goal on Day 3. Estimated goal was set at 25-35 nonprotein kcal/kg per day and 0.2 – 0.3 g nitrogen / kg per day at 72 hours post ICU admission. TPN was added to meet estimated requirements.
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Stable shock is not defined by weaning or removing all vasoactive agents.

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* 2009 Dec;35(Issue 12):2018-2027.

Doig GS, Chevrou-Severac H and Simpson F. Early enteral nutrition in critical illness: A full economic analysis using US costs. *ClinicoEconomics and Outcomes Research* **2013**;5:429-436.



Summary

Meta-analysis of all available trials demonstrate a **significant** reduction in mortality if EN is provided **within 24 h of ICU admission**.

Meta-analysis of all available trials demonstrate a **trend** towards a reduction in mortality if EN is provided **within 48h of ICU admission**.

There is no evidence of any mortality benefit if EN is commenced later than 48 h after ICU admission.

Indirect evidence from elective GI surgery patients demonstrates a **significant** reduction in mortality if EN is **commenced on the same day as surgery (< 24 h)**.

Furthermore, pneumonia, gut dysfunction, duration of mechanical ventilation and ICU stay may also be reduced if EN is commenced within 24 h of ICU admission.

Commence EN as soon as shock is stabilised



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How early is early?

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Research

Recherche

Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT)

Claudio M. Martin, Gordon S. Doig, Daren K. Heyland, Teresa Morrison, William J. Sibbald, for the Southwestern Ontario Critical Care Research Network

Abstract

Background: The provision of nutritional support for patients in intensive care units (ICUs) varies widely both within and between institutions. We tested the hypothesis that evidence-based algorithms to improve nutritional support in the ICU would improve patient outcomes.

Methods: A cluster-randomized controlled trial was performed in the ICUs of 11 community and 3 teaching hospitals between October 1997 and September 1998. Hospital ICUs were stratified by hospital type and randomized to the intervention or control arm. Patients at least 16 years of age with an expected ICU stay of at least 48 hours were enrolled in the study

If EN is preferable, starting sooner may be better. Data from the few animal and clinical studies on this topic support this hypothesis.⁷ However, recent observational studies have documented low rates of “optimal” use of EN in the critical care setting.⁸⁻¹⁰ EN is often started several days after admission, patients do not tolerate adequate amounts of EN, and PN is used excessively in some patients (up to 60% in some countries).⁸⁻¹⁰ Using an audit of intensive care units (ICUs) in community and teaching hospitals, our Critical Care Research Network (CCR-Net) also documented delays in the institution of nutritional support that included both enteral and parenteral routes.¹¹ Several studies have

Martin CM, Doig GS, Heyland DK, Morrison T and Sibbald WJ. Multicentre, cluster randomized clinical trial of algorithms for critical care enteral and parenteral therapy (ACCEPT). *CMAJ* 2004;170(2):197-204.



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Results: Two hospitals crossed over and were excluded from the primary analysis. Compared with the patients in the control hospitals ($n = 214$), the patients in the intervention hospitals ($n = 248$) received significantly more days of enteral nutrition (6.7 v. 5.4 per 10 patient-days; $p = 0.042$), had a significantly shorter mean stay in hospital (25 v. 35 days; $p = 0.003$) and showed a trend toward reduced mortality (27% v. 37%; $p = 0.058$). The mean stay in the ICU did not differ between the control and intervention groups (10.9 v. 11.8 days; $p = 0.7$).

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