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.



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

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



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Background: Review of the Guidelines

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

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Evidence of trend. Significant evidence. Significant evidence. Significant evidence.

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2015 Canadian guideline

< 48 h – Canadian guideline

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

	Early E	EN	Delayed/	None		Risk Ratio		Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.1.1 EN vs IV Fluids/N	o EN							
Moore	1	32	2	31	2.5%	0.48 [0.05, 5.07]	1986	· · · · · · · · · · · · · · · · · · ·
Chuntrasakul	1	21	3	17	2.9%	0.27 [0.03, 2.37]	1996	· · · · · · · · · · · · · · · · · · ·
Singh	4	21	4	22	8.7%	1.05 [0.30, 3.66]	1998	
Pupelis 2000	1	11	5	18	3.4%	0.33 [0.04, 2.45]	2000	· · · · · ·
Pupelis 2001	1	30	7	30	3.3%	0.14 [0.02, 1.09]	2001	<+
Malhotra	12	100	16	100	28.2%	0.75 [0.37, 1.50]	2004	
Subtotal (95% CI)		215		218	49.0%	0.62 [0.37, 1.05]		
Total events	20		37					
Heterogeneity: Tau ² = (0.00; Chi ²	= 4.10	, df = 5 (P :	= 0.54);	l² = 0%			
Test for overall effect: 2	Z = 1.78 (F	P = 0.0	8)					
1.1.2 EN vs Delayed EN	N							
Chiarelli	0	10	0	10		Not estimable	1990	
Ever	2	19	2	19	4.0%	1.00 [0.16, 6.38]	1993	
Kompan 1999	0	14	1	14	1.4%	0.33 [0.01, 7.55]	1999	· · · · · · · · · · · · · · · · · · ·
Minard	1	12	4	15	3.2%	0.31 [0.04, 2.44]	2000	· · · · · · · · · · · · · · · · · · ·
Kompan 2004	0	27	1	25	1.4%	0.31 [0.01, 7.26]	2004	←
Dvorak	0	7	0	10		Not estimable	2004	
Peck	4	14	5	13	11.8%	0.74 [0.25, 2.18]	2004	
Nguyen 2008	6	14	6	14	18.7%	1.00 [0.43, 2.35]	2008	
Moses	3	29	3	30	5.9%	1.03 [0.23, 4.71]	2009	
Chourdakis	3	34	2	25	4.7%	1.10 [0.20, 6.12]	2012	
Subtotal (95% CI)		180		175	51.0%	0.83 [0.49, 1.39]		
Total events	19		24					
Heterogeneity: Tau ² = 0	0.00; Chi ²	= 2.07	, df = 7 (P :	= 0.96);	l² = 0%			
Test for overall effect: 2	Z = 0.72 (F	P = 0.4	7)					
Total (95%CI)		395		393	100.0%	0.72 [0.50, 1.04]		•
Total events	39		61					
Heterogeneity: Tau ² = (0.00; Chi ²	= 6.83		= 0.91)	; l² = 0%			
Test for overall effect: 2								0.1 0.2 0.5 1 2 5 10
Test for subgroup differ				P = 0.44	4), l² = 0%			Favours Early EN Favours Delayed/None

• 16 clinical trials

- p=0.08 (trend)
- mortality reduction by 6%

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



< 48 h – 2016 ASPEN

	Early	EN	Delayed/	None		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% CI
Sagar 1979	0	15	0	15		Not estimable	1979	R
Aoore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]	1986	4 .
Chiarelli 1990	0	10	0	10		Not estimable	1990	
Schroeder 1991	0	16	0	16		Not estimable	1991	
Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]	1993	1 · · · · · · · · · · · · · · · · · · ·
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	• •
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	• • • • • • • • • • • • • • • • • • • •
Vatters 1997	0	14	0	14		Not estimable	1997	
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	1998	
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1999	• • •
linard 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	+
Ovorak 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	
1 alhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]	2004	
Vguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]	2008	+
loses 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	
fotal (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%			

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

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically III 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.



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



	Early	EN	Delayed/	None		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Sagar 1979	0	15	0	15		Not estimable	1979		
Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]	1986	+ .	-
Chiarelli 1990	0	10	0	10		Not estimable	1990		
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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	· · ·	
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	• • •	
Watters 1997	0	14	0	14		Not estimable	1997		
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	1998		
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1999	• • •	
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		
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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 = = 1.97 (P			= 0.95);	l² = 0%				5



Total 15 32 10 16 19 30 14 21 14 21 14 21 14 12 11	0 2 0 2 4 1 3 0 4 1 4	Total 15 31 10 16 19 30 14 17 14 22 14 15	2.3% 3.7% 4.9% 1.3% 2.7% 8.2% 1.3%		1979 1986 1990 1991 1993 1996 1996 1996 1997 1998 1999	
32 10 16 19 30 14 21 14 21 14 21 14 12	2 0 2 4 1 3 0 4 1 4	31 10 16 19 30 14 17 14 22 14	3.7% 4.9% 1.3% 2.7% 8.2% 1.3%	0.48 [0.05, 5.07] Not estimable Not estimable 1.00 [0.16, 6.38] 0.50 [0.10, 2.53] 0.33 [0.01, 7.55] 0.27 [0.03, 2.37] Not estimable 1.05 [0.30, 3.66] 0.33 [0.01, 7.55]	1986 1990 1991 1993 1996 1996 1996 1997 1998 1999	
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12	4	15		0 21 10 04 2 44	0000	Contract of the second s
11			3.0%	0.51 [0.04, 2.44]	2000	• • •
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	66					
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Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	Year	M-H. Random, 95% C1
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Chiarelli 1990	0	10	0	10		Not estimable	1990	
Schroeder 1991	0	16	0	16		Not estimable	1991	
Ever 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	• •
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	• • • • • • • • • • • • • • • • • • • •
Watters 1997	0	14	0	14		Not estimable	1997	
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	1998	
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1999	1 • • • • • • • • • • • • • • • • • • •
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: Tau² = 0 Test for overall effect: Z			and the second second second	= 0.95);	I ² = 0%			0.1 0.2 0.5 1 2 5 Favors Early EN Favors Delayed



- 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.



	Early		Delayed/			Risk Ratio					Risk	Rati	0		
Study or Subgroup	Events	Tota	Events	Tota	Weight	M-H. Random, 95% Cl	Year			М-Н.	Rane	lom.	95% C	1	_
Sagar 1979	0	15	0	15		Not estimable	1979								
Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]	1986	+			_			-	_
Chiarelli 1990	0	10	0	10		Not estimable	1990								_
Schroeder 1991	0	16	0	16		Not estimable	1991								
Ever 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]	1993		·		-	-			e.
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	+				-			-
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	+	_		_		_		
Watters 1997	0	14	0	14		Not estimable	1997								
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	1998			_	-	-	_	-	
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1999	+			_	-			-
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									1			
Heterogeneity: Tau² = 0 Test for overall effect: Z			and the second second second	= 0.95);	I²= 0%			0.1	0.2 Favo	0. rs Earl		1 Fav	2 ors De	5 layed	IN



		EN	Delayed	none		Risk Ratio		Risk Ratio
study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	Year	M-H. Random. 95% C
1 oore 1986	1	32	2	31	2.3%	0.48 (0.05, 5.07)	1986	
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Ever 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]	1993	
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Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]	2000	• • •
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fotal events	41		66					
Heterogeneity: Tau ² = 0.	.00; Chi ² =	7.23, 0	f = 15 (P =	= 0.95);	l ² = 0%			0.1 0.2 0.5 1 2

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 - Could not influence the difference in results between the 2015
 Canadian and 2016 ASPEN guideline results.
- Beier-Holgersen 1996

Gut 1996; 39: 833-835

833

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 Nutridrink 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 postoperatively.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

- Sagar 1979, Schroeder 1991 and Walters 1997 have zero deaths.
 - Could not influence the difference in results between the 2015
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- Beier-Holgersen 1996, Carr 1996

Gut 1996; 39: 833-835

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Influence of postoperative enteral nutrition on postsurgical infections

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

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

incidence of s diet infusion

operatively.2 In Abstract

enteral versus surgical patients receiving in clients who have underpatients receiving in the section is safe and effective. These investiga and therefore roperative enteral feeding through a masojejumal tube in Clinical Nut v conventional postoperative intravenous fluids until major surgery, 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 laparotomics 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."

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-

- Sagar 1979, Schroeder 1991 and Walters 1997 have zero deaths.
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 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.

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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



- Sagar 1979, Schroeder 1991 and Walters 1997 have zero deaths.
 - Could not influence the difference in results between the 2015

J Gastrointest Surg (2009) 13:569–575 DOI 10.1007/s11605-008-0592-x

Early Enteral	Nutrition With	nin 24 h of Ir	ntestinal Surgery
Mortality		~	· ~]
Beier-Holgersen 1996	2/30	4/30	
Carr 1996	0/14	1/14	
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: Chi^2 Test for overall effect: $Z = 2$		= 0%, p=0.988	
Test for overall effect. $Z = Z$.13 (F = 0.03)		



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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: Chi^2 Test for overall effect: $Z = 2$.	= 0.60, df = 5 (P = 0.	.99), l ² = 0%, p=0.988	



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Early Enteral	Nutrition	Within	24 h of	Intestinal	Surg	ery
Mortality					Ĵ	
Beier-Holgersen 1996	2/30		4/30	-		
Carr 1996	0/14		1/14			
Hartsell 1997	0/29		1/29			
Heslin 1997	2/97		3/98	-	₽∤	
Stewart 1998	0/40		1/40			
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Mortality	~		~	. ~	1	
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Carr 1996	0/14		1/14			
Hartsell 1997	0/29		1/29			
Heslin 1997	2/97		3/98	-	── ╸ ┤	
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	Early	EN	Delayed/None			Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% CI Y		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				
Ever 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]	1993			
Beier-Holgersen 1996	2	30	2	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	• •		
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	• • •		
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	1998			
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]	1999	• • •		
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 =	723 (If = 15 (P :	- 0.95	12 - 0%			0.1 0.2 0.5 1 2		



	Early	EN	Delayed	None		Risk Ratio		Risk Ratio		
Study or Subgroup	Events		Events		Weight	M-H. Random, 95% Cl	Year	M-H. Random. 95% Cl		
Moore 1986	1	32	2	31	2.3%	0.48 (0.05, 5.07)	1986	· · ·		
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Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]	2000	+ · · ·		
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Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]	2012	1		
Total (95% CI)		469		467	100.0%	0.70 [0.49, 1.00]		-		
Total events	41		66							



	Early	EN	Delayed	None		Risk Ratio		Risk Ratio
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Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	1996	• · · · · · · · · · · · · · · · · · · ·
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Total (95% CI)		469		467	100.0%	0.70 [0.49, 1.00]		-
Total events	41		66					
Heterogeneity: Tau ² = 1 Test for overall effect: 2	0.00; Chi ² =		df = 15 (P :	= 0.95);	I ² = 0%			0.1 0.2 0.5 1 2 5 10 Favors Early EN Favors Delayed/None



Ch. I C. I		EN	Delayed	None		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	Year	M-H. Random, 95% CI
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Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]	2004	· · · ·
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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)		395		393	100.0%	0.72 [0.50, 1.04]		
Total events	39)	61					
Heterogeneity: Tau ²	= 0.00; Chi	i² = 6.83	3, df = 13 (l	P = 0.91)	; I² = 0%			
Test for overall effect								0.1 0.2 0.5 1 2 5 10 Favours Early EN Favours Delayed/None

- 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.

- The concept of 'early' enteral feeding was popularised in the mid '80s.
- Five major clinical practice guidelines recommend *early* EN.
- < 48 h Canadian guideline,
- < 24 h ACCEPT guideline (also Canadian),
- < 24 h Australian and New Zealand guideline,
- < 24 h European (ESPEN) guideline and
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Evidence of trend. Significant evidence. Significant evidence. Significant evidence. Evidence of trend.

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- 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.
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- The concept of 'early' enteral feeding was popularised in the mid '80s.
- Five major clinical practice guidelines recommend *early* EN.
- < 48 h Canadian guideline,
- < 24 h ACCEPT guideline (also Canadian),
- < 24 h Australian and New Zealand guideline,
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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



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.



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

Study or sub-category	early EN (<24 h) n/N	Control n/N	OR (fixed) 95% Cl	Weight %	OR (fixed) 95% CI
Chiarelli 1990 Kompan 1999	0/10 0/17	0/10 2/19		- 13.40	Not estimable 0.20 [0.01, 4.47]
Kompan 2004	0/27	1/25		8.89	0.30 [0.01, 7.63]
Nguyen 2008 Chuntrasakul 1996	6/14 1/21	6/14 3/17		- 19.95 18.38	1.00 [0.22, 4.47] 0.23 [0.02, 2.48]
Pupelis 2001	1/30	7/30		39.38	0.11 [0.01, 0.99]
Total (95% CI) Total events: 8 (early EN (<2 Test for heterogeneity: Chi ² = Test for overall effect: Z = 2.3	= 3.20, df = 4 (P = 0.52), l ² = 0%	115		100.00	0.34 [0.14, 0.85]
			0.1 0.2 0.5 1 2 Favours EN Favours Co	5 10	

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



Results: Primary MA, Pneumonia

Review: Comparison: Outcome:	Early EN (<24h) vs Control (Primary Analysis) 01 early EN vs Control 02 Pneumonia, Intention to treat analysis)						
Study or sub-category	early EN (<24 h) n/N	Control n/N		OR (1 95%	fixed) % CI		Weight %	OR (fixed) 95% Cl
Kompan 2004 Nguyen 2008	9/27 3/14	16/25 6/14					70.15 29.85	0.28 [0.09, 0.88] 0.36 [0.07, 1.91]
Test for heterog	41 (early EN (<24 h)), 22 (Control) eneity: Chi ² = 0.06, df = 1 (P = 0.80), l ² = 0% effect: Z = 2.47 (P = 0.01)	39					100.00	0.31 [0.12, 0.78]
			0.01 Favo	0.1 urs treatment		10 s control	100	

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



Gut dysfunction

Review: Comparison: Outcome:	Early EN (<24h) vs Standard Care 01 early EN vs Standard Care 03 Complications (Gut Dysfunction)					
Study or sub-category	Early EN n/N	Delayed EN n/N		Peto OR 95% CI	Weight %	Peto OR 95% Cl
Chiarelli 1990 Kompan 2004 Pupelis 2001	1/10 19/27 2/30	2/10 20/25 6/30	• • •	•	13.65 50.49 35.86	0.47 [0.04, 5.19] 0.60 [0.17, 2.10] 0.32 [0.07, 1.41]
Test for heteroge	⁶⁷ (Early EN), 28 (Delayed EN) eneity: Chi ² = 0.41, df = 2 (P = 0.81), l ² = 0% effect: Z = 1.69 (P = 0.09)	65			100.00	0.47 [0.19, 1.13]
			0.1 0.2 0 Favours treat	-	5 10 s control	

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
Study or subgroup	E Mean [days]	EEN SD [days]	Total		SoC SD [days]	Total	Weight	Mean difference IV, fixed, 95% CI [days]	Year	Mean difference IV, fixed, 95% CI [days]
Chuntrasakul et al ¹⁸	8.14	6.28	21	8.35	4.78	17	47.7%			
								-0.21 [-3.73, 3.31]	1996	- T
Pupelis et al ¹⁹	13.9	14.6	30	16	20.5	30	7.3%	-2.10 [-12.86, 8.66]	2001	
Kompan et al ²⁰	15.9	9.7	27	20.6	18.5	25	8.9%	-4.70 [-12.82, 3.42]	2004	
Nguyen et al ²¹	11.3	2.99	14	15.9	7.11	14	36.1%	-4.60 [-8.64, -0.56]	2008	
Total (95% CI)			92			86	100.0%	-2.34 [-4.76, 0.09]		•
										-10 -5 0 5 10
										Favors EEN Favors SoC

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); $l^2 = 0$ %. Test for overall effect: Z = 1.87 (P = 0.06).

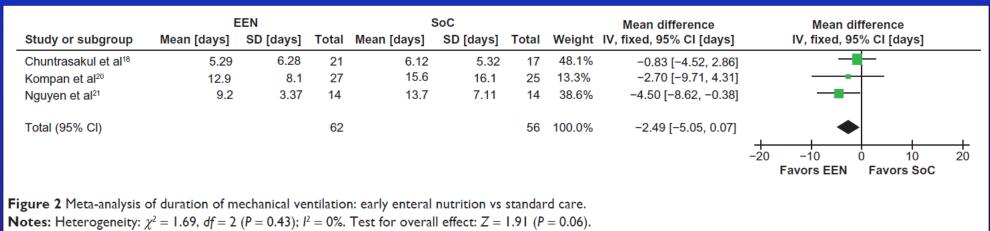
Abbreviations: CI, confidence interval; EEN, early enteral nutrition; ICU, Intensive Care Unit; IV, inverse variance; SD, standard deviation; SoC, standard of care.

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

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.



Duration of MV



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

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

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.



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



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- Early feeding resulted in a significant decrease in:
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- Early feeding resulted in a significant decrease in:
 - Mortality (2.4% eEN vs 6.9%, p=0.03)
- Early feeding was not associated with any harms:
 - Wound infections (7.1% eEN vs 9.3%, p=0.26)
 - Anastomotic dehiscence (2.8% eEN vs 4.3%, p=0.27)
 - Pneumonia (2.3% eEN vs 3.3%, p=0.46)

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"There is no obvious benefit for keeping patients "nil by mouth" after gastrointestinal surgery"







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



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).



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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.



Study	Patient population	Early EN intervention
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- Shock Index ≤ 1 (Heart rate / SBP) for one hour or
- SBP > 100 mmHg without need for *increasing* doses of vasoactive agents for one hour.

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.



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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Early EN defined as within 24 hours of injury or ICU admission

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



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CMAJ 2004;170(2):197-204

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