Early Enteral Nutrition in critical illness: Why?

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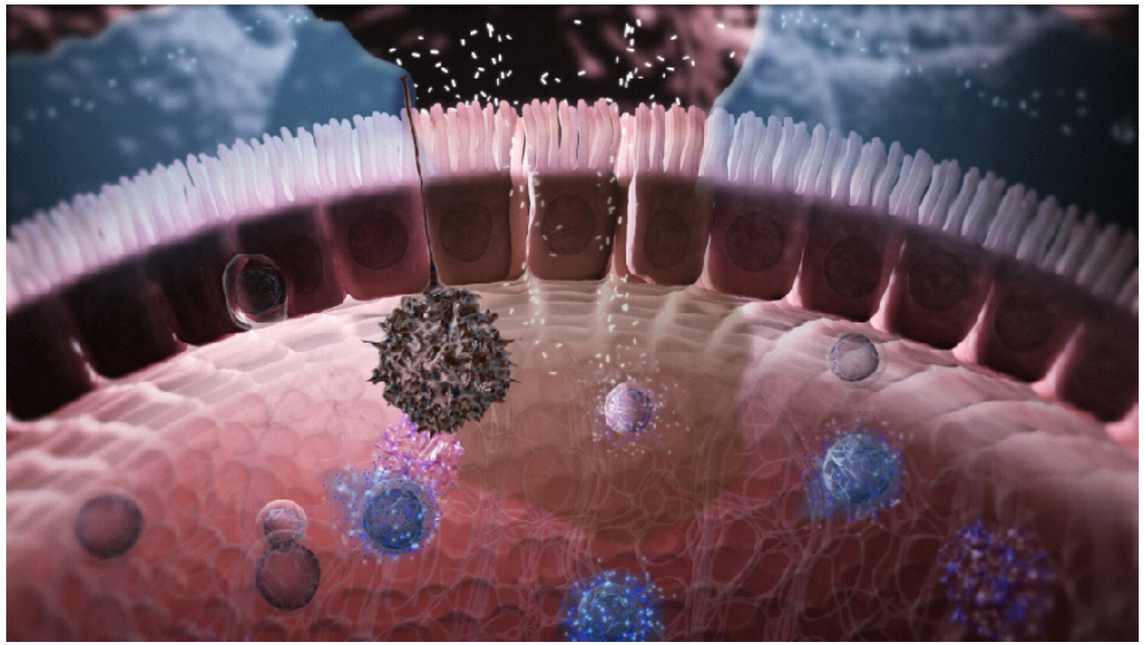
What is Early Enteral Nutrition?

Why Early Enteral Nutrition?

- To maintain intestinal mucosal integrity
- Provide nutrients required during metabolic stress
- Reduce morbidity compared with parenteral nutrition
- Reduce cost compared with parenteral nutrition



Enteral nutrition initiated within 24-48 hours following hospitalization, trauma, or injury

Zaloga GP. Crit Care Med 1999;27:259
Alverdy Crit Care Med 2003;31:598

Why would you like to start early with Early Enteral Nutrition?

Calories received in high and low risk patients based on NUTRIC scores and 28-day mortality

Table 1: NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50 - <75	1
	≥75	2
APACHE II	<15	0
	15 - <20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6 - <10	1
	≥10	2
Number of Co-morbidities	0-1	0
	≥2	1
Days from hospital to ICU admission	0 - <1	0
	≥1	1
IL-6	0 - <400	0
	≥ 400	1

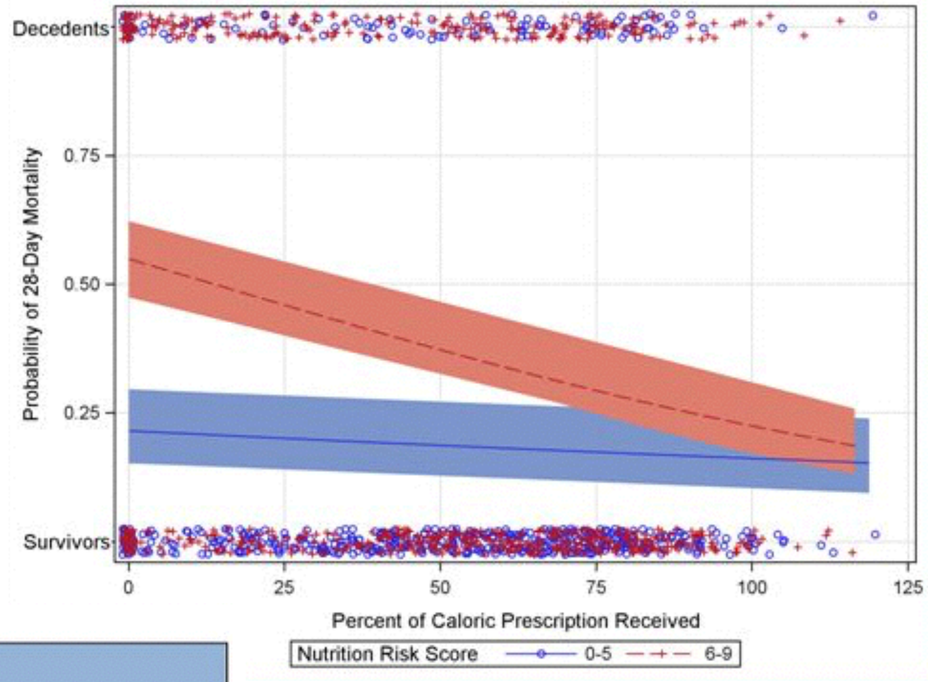


Table 2: NUTRIC Score scoring system: if IL-6 available

Sum of points	Category	Explanation
6-10	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-5	Low Score	➢ These patients have a low malnutrition risk.

Table 3. NUTRIC Score scoring system: If no IL-6 available*

Sum of points	Category	Explanation
5-9	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-4	Low Score	➢ These patients have a low malnutrition risk.

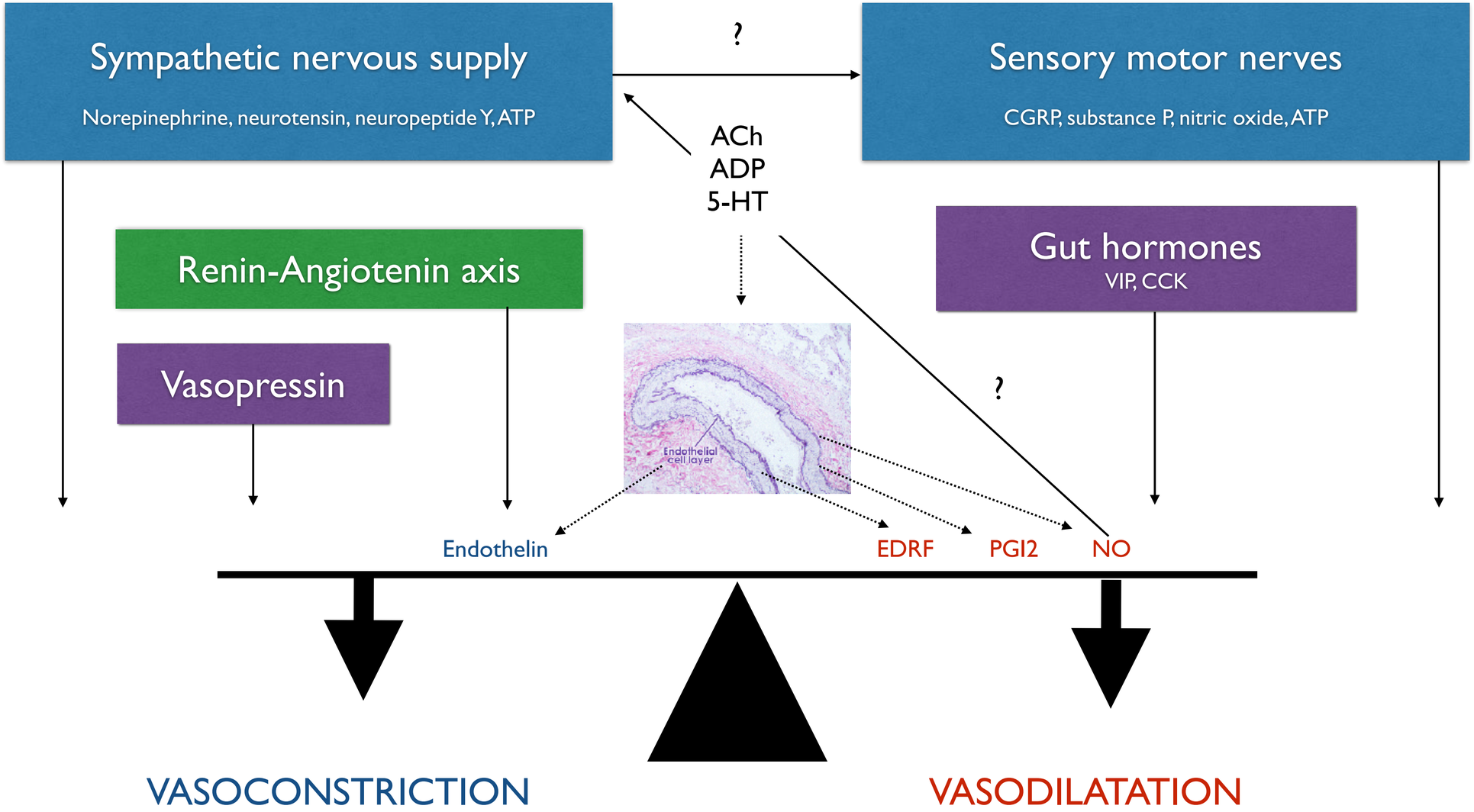
Rahman A et al. Clin Nutr. 2016 Feb;35(1):158-62.

More Protein and Energy Associated With Improved Mortality in Higher Risk Patients

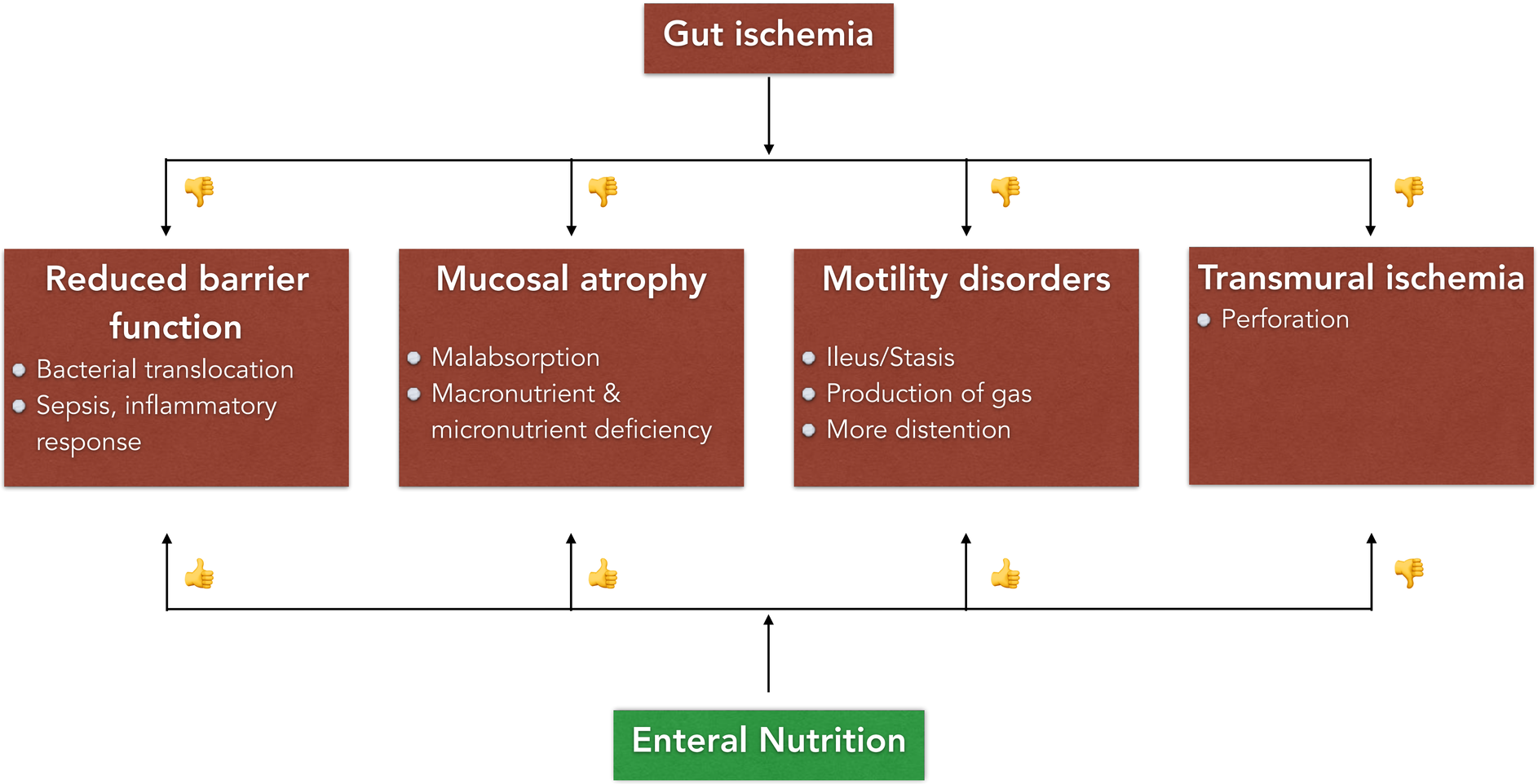
Outcome	Protein Intake (per 10% of Goal)		Energy Intake (per 10% of Goal)	
	Low NUTRIC Score (n = 1,217)	High NUTRIC Score (n = 1,636)	Low NUTRIC Score (n = 1,217)	High NUTRIC Score (n = 1,636)
Sample in ICU ≥ 4 d				
Mortality[a,b]	0.952 (0.895–1.011)	0.930 (0.892–0.969)[c]	0.962 (0.904–1.023)	0.927 (0.893–0.962)[c]
Adjusted[d]	0.998 (0.936–1.064)	0.934 (0.894–0.975)[c]	1.011 (0.946–1.079)	0.929 (0.893–0.966)[c]
TDA[f,g]	0.970 (0.936–1.006)	1.004 (0.967–1.043)	0.956 (0.921–0.992)[c]	0.995 (0.959–1.032)[c]
Adjusted[d]	1.013 (0.975–1.052)	1.051 (1.012–1.091)[c]	0.998 (0.958–1.039)	1.045 (1.007–1.085)[c]
Sample in ICU ≥ 12 d				
Mortality[a,b]	1.059 (0.964–1.165)	0.913 (0.853–0.977)[e]	1.069 (0.975–1.173)	0.909 (0.854–0.967)[e]
Adjusted[d]	1.052 (0.954–1.156)	0.899 (0.84–0.963)[e]	1.067 (0.967–1.178)	0.884 (0.829–0.941)[c]
TDA [f,g]	0.963 (0.913–1.016)	1.062 (1.002–1.126)[e]	0.937 (0.888–0.989)[e]	1.048 (0.990–1.109)
Adjusted[d]	0.999 (0.946–1.056)	1.092 (1.032–1.155)[e]	0.981 (0.925–1.040)	1.091 (1.032–1.155)[e]

Compher C et al. Crit Care Med 2017; 45:156–163

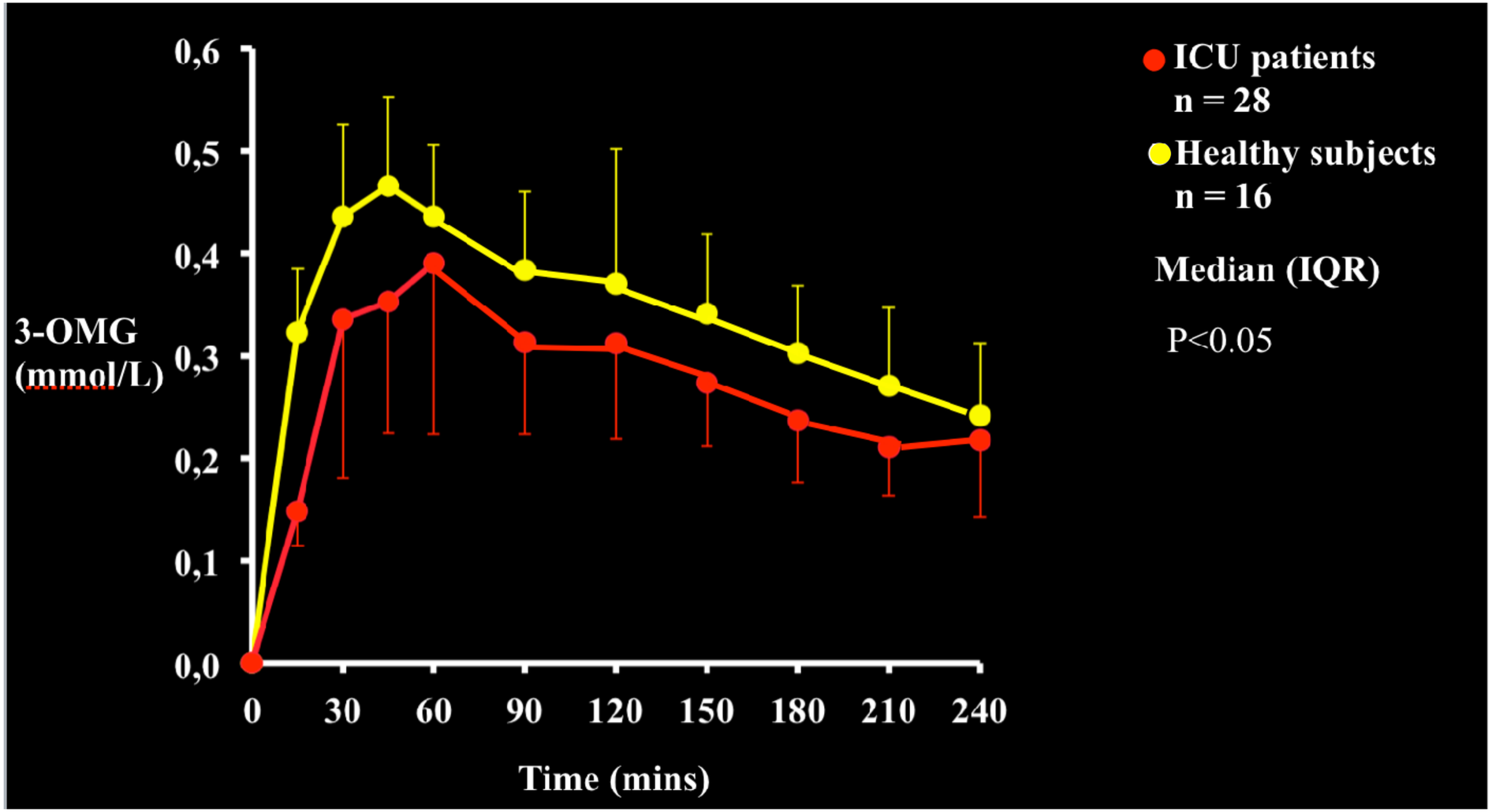
Factors in regulation of splanchnic circulation



Enteral nutrition and splanchnic ischemia



Small intestinal glucose absorption in critical illness versus health



Deane, et al. Crit. Care Med 2011

Delayed EN impairs intestinal carbohydrate absorption in ICU patients

impact of delayed EN on small intestinal absorption of 3-O-methyl-glucose: Gastric emptying (scintigraphy)

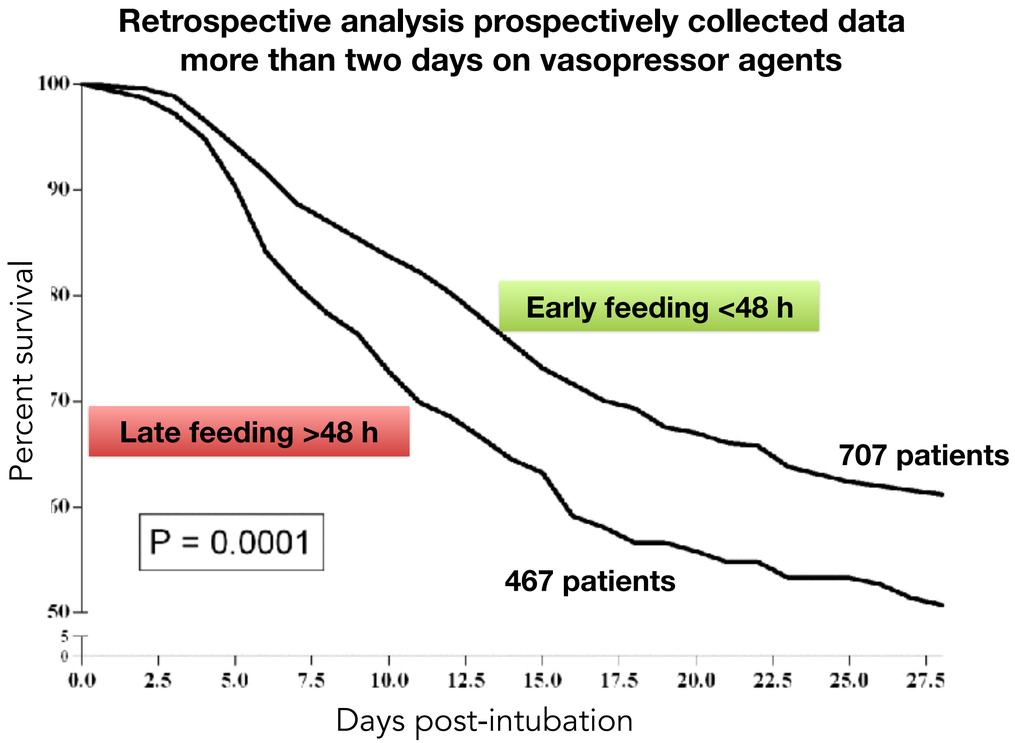
	Enteral nutrition < 24 hours N= 14	Enteral nutrition > 4 days N=14	P-value
3-O-methyl-glucose day 4			
Peak	0.37 ± 0.04	0.24 ± 0.04	P < 0.02
AUC 240 min	63.4 ± 8.3	38.5 ± 7.0	P < 0.04
Mechanical ventilation			
Days	9.2 ± 0.9	13.7 ± 1.9	P < 0.05
ICU length of stay			
Days	11.3 ± 0.8	15.9 ± 1.9	P < 0.05

Delaying enteral feeding is associated with a reduction in small intestinal glucose absorption
These observations support recommendations for "early" enteral nutrition in critically ill patients

Nguyen N. Crit Care Med. 2012;40(1):50-4

Is Early Enteral Nutrition safe when the ICU patient is on vasopressors?

Safe on vasopressors?



Patients at least 1 vasopressor significant better survival when feeding is commenced early

Khalid I. Am J Crit Care. 2010;19:261-268

Is Early Enteral Nutrition safe in with early shock?

Enteral vs Parenteral nutrition in ventilated shock patients: NUTRIREA-2

	Enteral group (n=1202)	Parenteral group (n=1208)	Absolute difference estimate (95% CI)	Hazard ratio (95% CI)	p value
Primary outcome					
Day 28 mortality	443/1202 (37%)	422/1208 (35%)	2·0 (−1·9 to 5·8)	..	0·33
Secondary outcomes					
Day 90 mortality	530/1185 (45%)	507/1192 (43%)	2·2 (−1·8 to 6·2)	..	0·28
ICU mortality*	429 (33%)	405 (31%)	..	1·10 (0·96 to 1·26)	0·17
Hospital mortality*	498 (36%)	479 (34%)	..	1·08 (0·95 to 1·22)	0·25
ICU length of stay (days)	9·0 (5·0 to 16·0)	10·0 (5·0 to 17·0)	..	..	0·08
Acute-care hospital length of stay (days)	17·0 (8·0 to 32·0)	18·0 (9·0 to 33·0)	..	..	0·11
Days without vasopressor support*	20·0 (0·0 to 25·0)	21·0 (0·0 to 26·0)	..	..	0·10
Days without dialysis*	27·0 (0·0 to 28·0)	27·0 (0·0 to 28·0)	..	..	0·52
Days without mechanical ventilation*	11·0 (0·0 to 23·0)	12·0 (0·0 to 23·0)	..	..	0·54
Infections					
ICU-acquired infection*	173 (14%)	194 (16%)	..	0·89 (0·72 to 1·09)	0·25
Ventilator-associated pneumonia*	113 (9%)	118 (10%)	..	0·96 (0·74 to 1·24)	0·75
Bacteraemia*	38 (3%)	55 (5%)	..	0·69 (0·46 to 1·04)	0·08
CVC-related infection*	29 (2%)	27 (2%)	..	1·07 (0·64 to 1·81)	0·79
Urinary tract infection*	18 (2%)	16 (1%)	..	1·13 (0·58 to 2·21)	0·73
Soft-tissue infection					
Patients (n)	1/1202	6/1208	..	..	..
Other infection*	11 (1%)	21 (2%)	..	0·52 (0·25 to 1·09)	0·08
Gastrointestinal complications					
Vomiting*	406 (34%)	246 (24%)	..	1·89 (1·62 to 2·20)	<0·0001
Diarrhoea*	432 (36%)	393 (33%)	..	1·20 (1·05 to 1·37)	0·009
Bowel ischaemia*	19 (2%)	5 (<1%)	..	3·84 (1·43 to 10·3)	0·007
Acute colonic pseudo-obstruction*	11 (1%)	3 (<1%)	..	3·7 (1·03 to 13·2)	0·04

In critically ill adults with shock, early isocaloric enteral nutrition did not reduce mortality or the risk of secondary infections but was associated with a greater risk of digestive complications compared with early isocaloric parenteral nutrition.

Reignier J et al. Lancet Published online November 8, 2017

Gastrointestinal complications of EN in early shock: NUTRIREA-2

Gastrointestinal complications					
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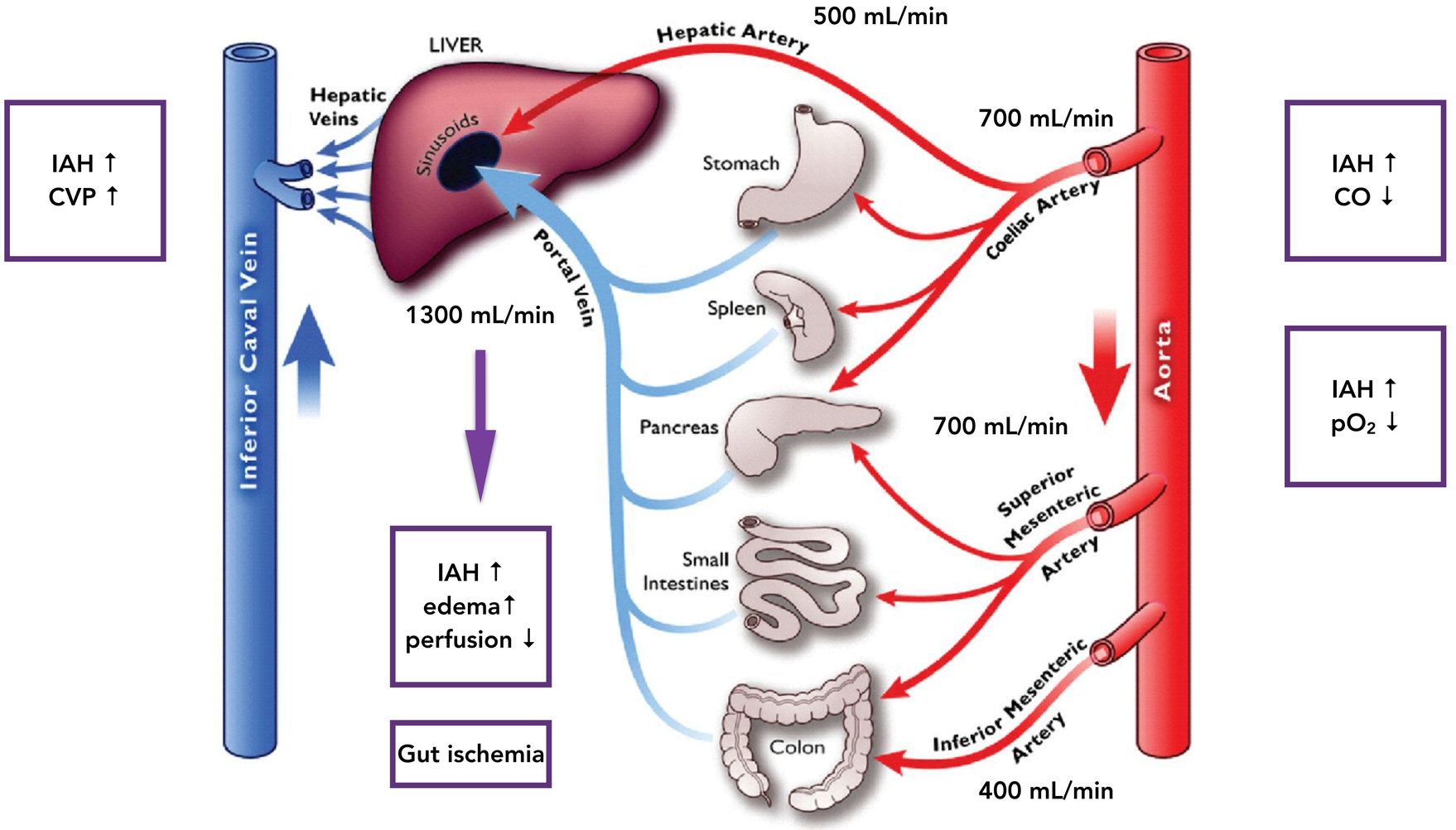
Comment on Nutrirea II study

- **Patients in severe shock**
- **High vasopressor dosages**
- **Early aggressive build-up of enteral feeding to target within 24-28 hours**
- **ESICM guidelines 2018:**

> **Recommendation 2. We suggest delaying EN if shock is uncontrolled and haemodynamic and tissue perfusion goals are not reached, but start low dose EN as soon as shock is controlled with fluids and vasopressors/ inotropes (Grade 2D).**

Is Early Enteral Nutrition safe in patients with intra-abdominal hypertension?

Splanchnic Circulation in abdominal hypertension



IAH/IAC and EEN

Author Year	Population No of pt studied	Study design	Feeding details	Groups in comparison	Main outcomes
Cothren 2004 [100]	Abdominal compartment syndrome after trauma N=37	Retrospective case series	12 pt were not fed, 25 were fed, but EN was started 5.1±1.9 d after injury	None	MOF rate 24% (9 of 37 patients), mortality 38% (14 of 37 patients). EN in 25 of 37 patients: in 13 ≤24 h after abd. closure, 7 patients delayed, 5 patients were fed despite open abdomen. In the 13 of ≤24 h fed patients, EN was started on postinjury day 5.1±1.9.
Reintam 2008 [112]	ICU patients on mechanical ventilation and with LOS>24h N=264	Prospective case series	No protocol	None	ACS developed in 1.8%
Reintam 2008 [113]	General ICU patients on mechanical ventilation at risk for IAH N=257	Prospective case series	No protocol	None	IAH developed in 37%, only 14% of them received EN

Sun 2013 [114]	Severe acute pancreatitis N=60	Prospective cohort	Early EN within 48h; delayed EN from day 8 on	Early vs delayed EN
				
				IAP<15 mmHg vs IAP ≥15 mmHg
					IAH incidence from the 9th day after admission: EEN 8/30 versus delayed EN 18/30; P = 0.009.
					FI incidence during the initial 3 days of feeding:
					day 1: EEN 25/30 versus DEN 12/30; P = 0.001;
					day 2: EEN 22/30 versus DEN 9/30; P = 0.001;
					day 3: EEN 15/30 versus DEN 4/30; P = 0.002.
					Patients with an IAP <15 mmHg had lower FI incidence than those with

Reintam A, Van Zanten AR et al. Intensive Care Med. 2017 Mar;43(3):380-398

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R 2					
R 2	N=257				

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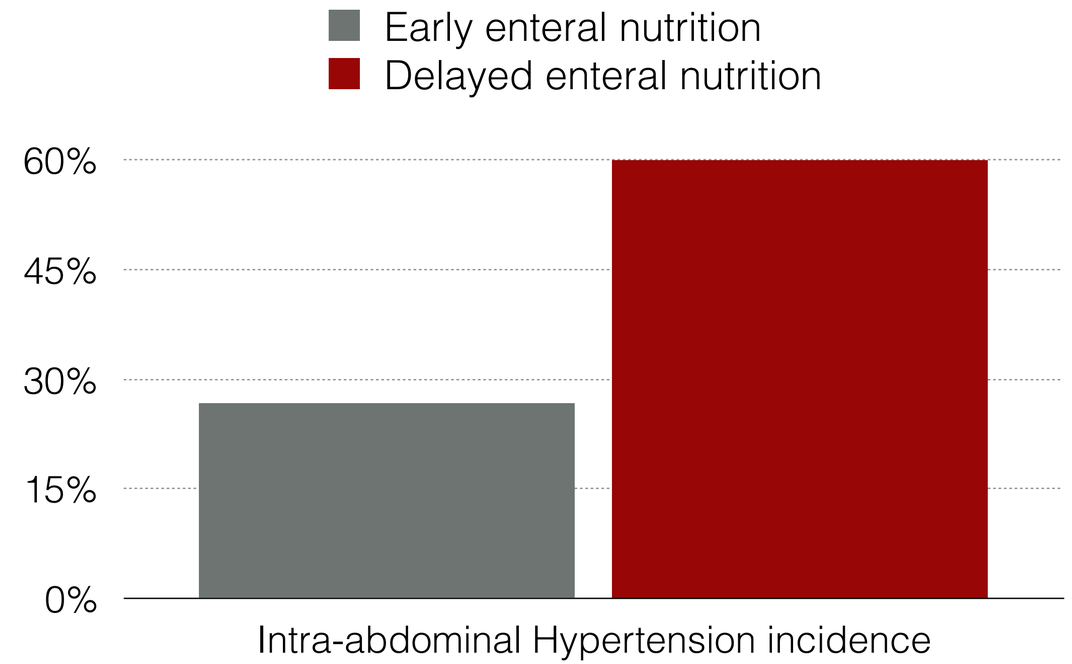
All studies reported high incidence of feeding intolerance associated with intra-abdominal hypertension, but data are not conclusive regarding causality. A recently published study demonstrated that EEN did not increase intra-abdominal pressure, but values exceeding 15 mmHg were associated with higher rates of feeding intolerance in patients with severe acute pancreatitis

Reintam A, Van Zanten AR et al. Intensive Care Med. 2017 Mar;43(3):380-398

EEN prevents IAH and reduces severity of SAP compared with delayed EN

Severe Acute Pancreatitis

EEN group (n=30): 8 h
DEN (n=30): day 8
Observation 2 weeks



Early enteral nutrition did not increase IAP.
In contrast, it might prevent the development of IAH.

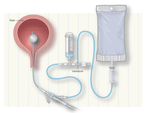
Sun J, et al. World Journal of Surgery. 2013, 37: 2053–2060.

Early Enteral Nutrition in IAH and ACS

Flow chart for high risk increased intra-abdominal pressure patients

Delay EEN in case of:
- Uncontrolled shock
- Overt bowel ischemia
- High-output fistula that cannot be bypassed
- Abdominal compartment syndrome

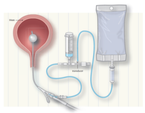
ICU admission → Start EEN



Delay EEN in case of:
- GRV>500 mL/6h
- Insert post pyloric feeding tube
- Administer prokinetics
- Monitor abdominal pressures

IAP ≥15 mmHg

Delay or reduce EEN:
- When during IAH and EEN administration IAP increases ≥15 mmHg
- Monitor IAP and criteria of ACS
- Interrupt feeding in ACS



Resume EN:
In case of EN intolerance or not reaching goals:
Consider SPN in high nutritional risk patients (day 3-5)
In low risk patients delay SPN until day 7

Abdominal Compartment Syndrome → Open abdomen

Sustained IAP ≥ 20 mmHg and organ failure

Can we predict splanchnic ischemia to safely start EEN?

Intern Emerg Med (2017) 12:821–836
DOI 10.1007/s11739-017-1668-y

EM - REVIEW

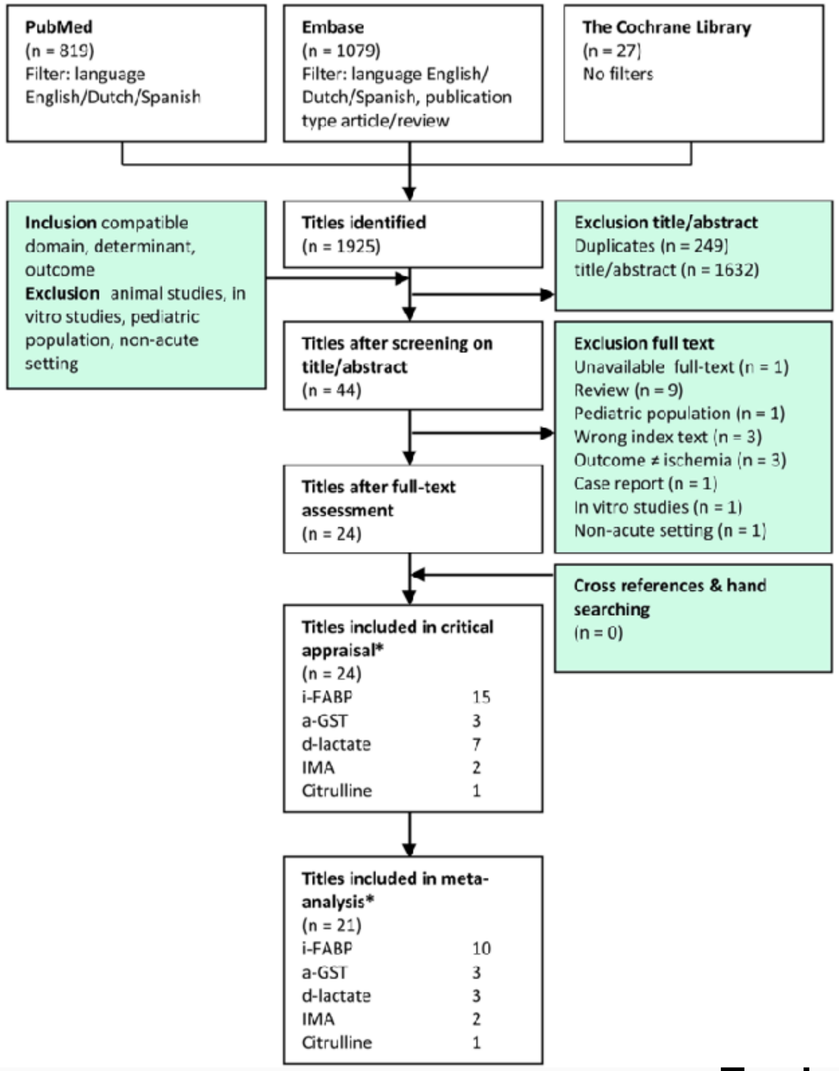
Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis

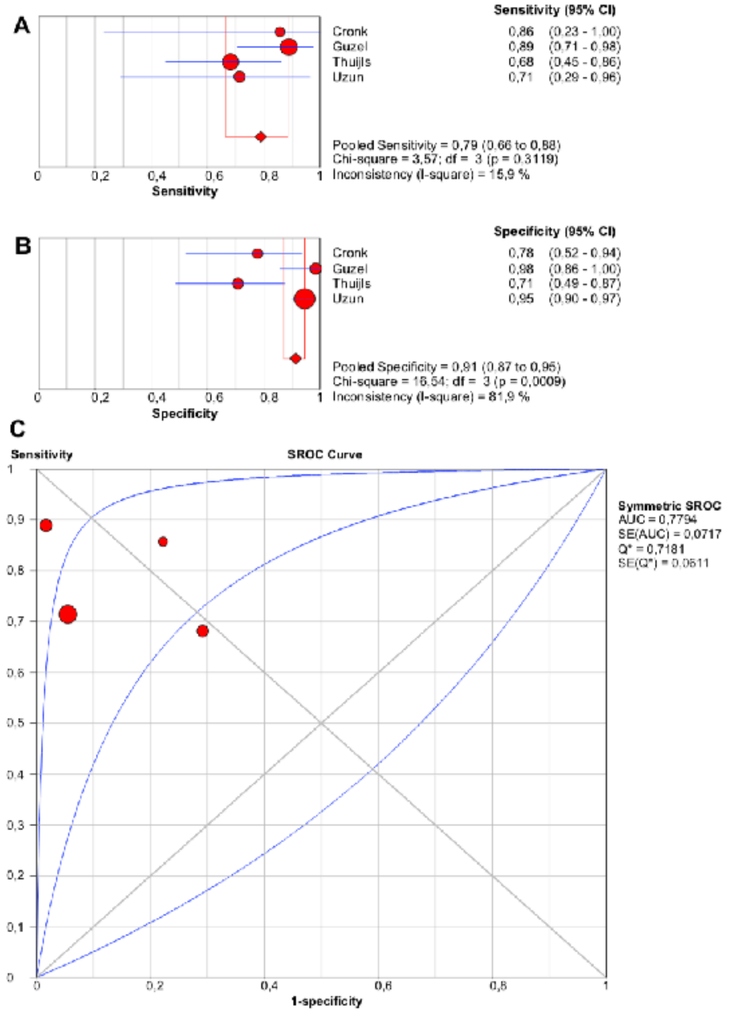
Nikki Treskes[1] · Alexandra M. Persoon[2] · Arthur R. H. van Zanten[1]

I-FABP, D-lactate, α-Glutathione S-transferase (α-GST), and Ischemia-modified albumin (IMA)

Treskes N, Persoon AM, Van Zanten AR. Intern Emerg Med (2017) 12:821–836

Biomarkers for splanchnic ischemia





Treskes N, Persoon AM, Van Zanten AR. Intern Emerg Med (2017) 12:821–836

Biomarkers for splanchnic ischemia

	No. of studies	Sensitivity	I^2 (%)	p value	Specificity	I^2 (%)	p value	Positive LR[a]	I^2 (%)	p value	Negative LR	I^2 (%)	p value
I-FABP (Uden kit)	4	0.790 (0.665–0.885)	16	0.312	0.913 (0.870–0.946)	82	0.001	6.368 (2.100–18.534)	79	0.003	0.262 (0.130–0.543)	41	0.146
I-FABP (Osaka kit)	6	0.750 (0.679–0.812)	0	0.463	0.792 (0.762–0.820)	87	0.000	4.577 (2.910–7.197)	75	0.001	0.321 (0.249–0.413)	0	0.629
D-lactate	3	0.717 (0.586–0.825)	20	0.288	0.742 (0.690–0.790)	98	0.000	3.621 (0.770–17.035)	97	0.000	0.371 (0.249–0.552)	0	0.845
α-GST	3	0.678 (0.542–0.795)	88	0.000	0.842 (0.753–0.909)	0	0.792	3.27 (1.50–7.16)	27	0.252	0.40 (0.11–1.49)	90	0.000
IMA	2	0.947 (0.740–0.999)	0	0.739	0.864 (0.651–0.971)	0	0.906	6.931 (2.37–24.24)	0	0.935	0.064 (0.02–0.48)	0	0.742

Numbers between brackets represent 95% confidence intervals

I^2 inconsistency (I-square)

[a] Likelihood ratio

- Best pooled performance IMA and I-FABP (Uden kit).
- Citrulline promising marker with high reported specificity (1 study).
- Heterogeneous and small patient populations studied.
- Positive and negative predictive values do not demonstrate optimal performance.
- Too early to consider them to replace other diagnostic modalities such as CT angiography.

Treskes N, Persoon AM, Van Zanten AR. Intern Emerg Med (2017) 12:821–836

What to do? What do the guidelines tell us?

Recent guidelines Open Access

Intensive Care Med (2017) 43:380–398
DOI 10.1007/s00134-016-4665-0

CONFERENCE REPORTS AND EXPERT PANEL

Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines

Annika Reintam Blaser[1,2*], Joel Starkopf[1,3], Waleed Alhazzani[4,5], Mette M. Berger[6], Michael P. Casaer[7], Adam M. Deane[8], Sonja Fruhwald[9], Michael Hiesmayr[10], Carole Ichai[11], Stephan M. Jakob[12], Cecilia I. Loudet[13], Manu L. N. G. Malbrain[14], Juan C. Montejo González[15], Catherine Paugam-Burtz[16], Martijn Poeze[17], Jean-Charles Preiser[18], Pierre Singer[19,20], Arthur R.H. van Zanten[21], Jan De Waele[22], Julia Wendon[23], Jan Wernerman[24], Tony Whitehouse[25], Alexander Wilmer[26], Heleen M. Oudemans-van Straaten[27] and ESICM Working Group on Gastrointestinal Function

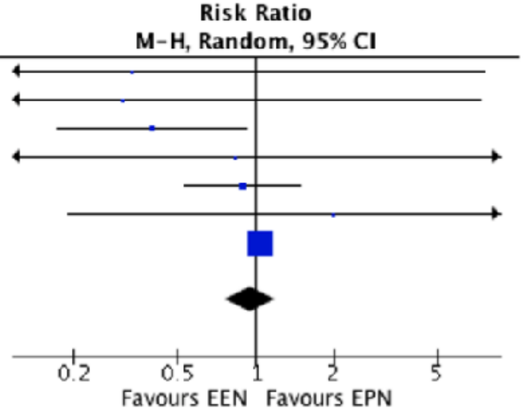
EEN ESICM Practice Guidelines 2017

a Mortality

Study or Subgroup	EEN Events	EEN Total	EPN Events	EPN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kompan 1999	0	14	1	14	0.5%	0.33 [0.01, 7.55]	1999
Kompan 2004	0	27	1	25	0.5%	0.31 [0.01, 7.26]	2004
Lam 2007	6	41	15	41	6.5%	0.40 [0.17, 0.93]	2007
Justo Meirelles 2011	1	12	1	10	0.7%	0.83 [0.06, 11.70]	2011
Altintas 2011	13	30	20	41	15.5%	0.89 [0.53, 1.49]	2011
Sun 2013	2	30	1	30	0.9%	2.00 [0.19, 20.90]	2013
Harvey 2014	450	1186	431	1185	75.4%	1.04 [0.94, 1.16]	2014
Total (95% CI)		**1340**		**1346**	**100.0%**	**0.95 [0.76, 1.19]**	
Total events	472		470				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.60$, df = 6 (P = 0.36); $I^2 = 9\%$

Test for overall effect: Z = 0.46 (P = 0.64)



Early EN vs. Early PN

b Infections

Study or Subgroup	EEN Events	EEN Total	EPN Events	EPN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moore 1989	1	29	6	30	4.1%	0.17 [0.02, 1.35]	1989
Kompan 2004	9	27	16	25	18.5%	0.52 [0.28, 0.96]	2004
Lam 2007	10	41	25	41	18.8%	0.40 [0.22, 0.72]	2007
Altintas 2011	7	30	13	41	15.1%	0.74 [0.33, 1.62]	2011
Justo Meirelles 2011	2	12	4	10	7.0%	0.42 [0.10, 1.82]	2011
Sun 2013	3	30	10	30	9.5%	0.30 [0.09, 0.98]	2013
Harvey 2014	251	1195	261	1188	26.9%	0.96 [0.82, 1.11]	2014
Total (95% CI)		**1364**		**1365**	**100.0%**	**0.55 [0.35, 0.86]**	
Total events	283		335				

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 17.26$, df = 6 (P = 0.008); $I^2 = 65\%$

Test for overall effect: Z = 2.60 (P = 0.009)

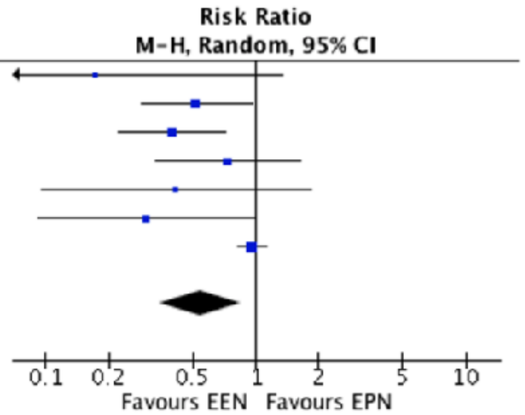
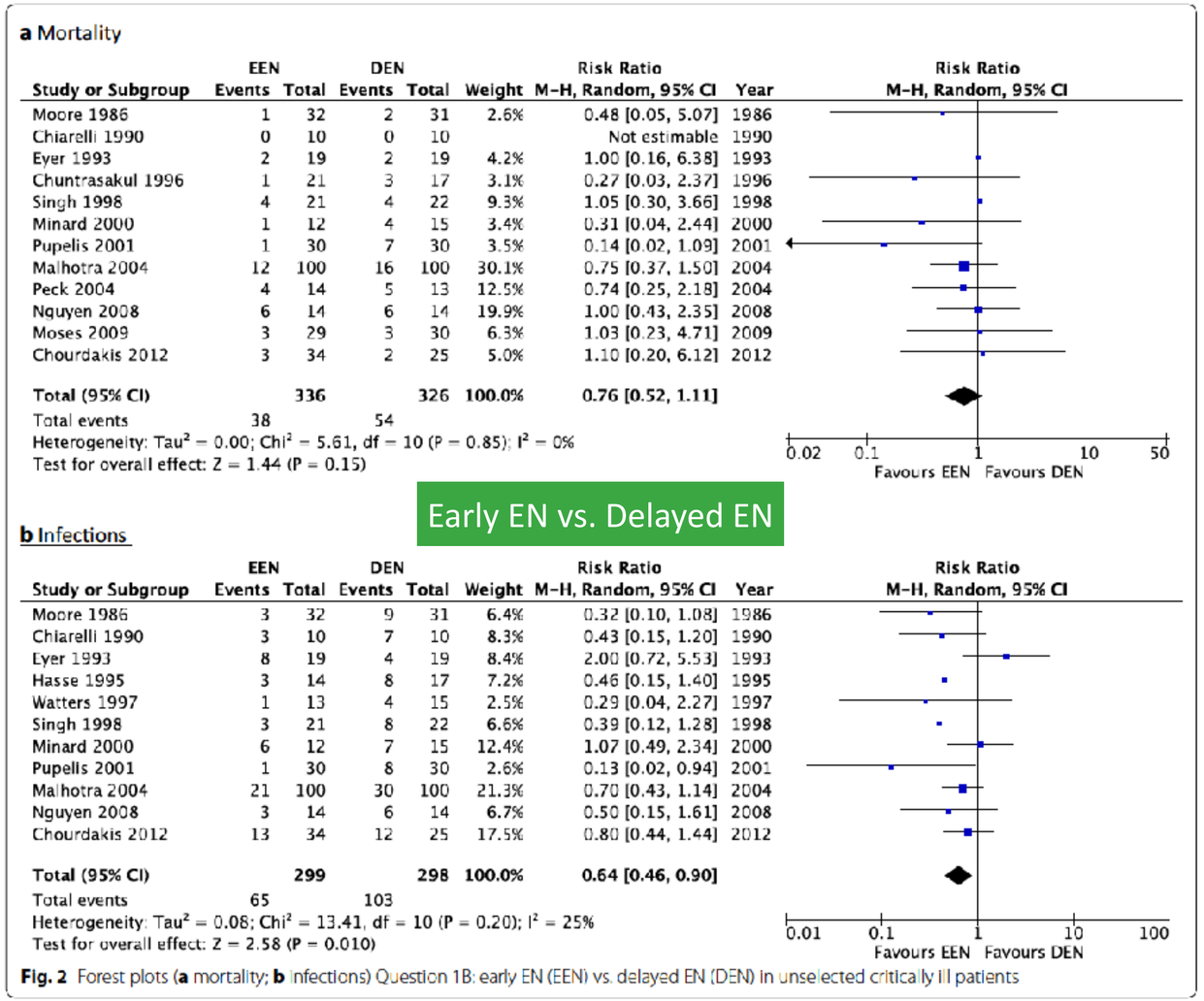


Fig. 1 Forest plots (**a** mortality; **b** infections) Question 1A: early EN (EEN) vs. early PN (EPN) in unselected critically ill patients

Reintam A, Van Zanten AR et al. Intensive Care Med. 2017 Mar;43(3):380-398

EEN ESICM Practice Guidelines 2017



a Mortality

Study or Subgroup	EEN Events	EEN Total	DEN Events	DEN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moore 1986	1	32	2	31	2.6%	0.48 [0.05, 5.07]	1986
Chiarelli 1990	0	10	0	10		Not estimable	1990
Eyer 1993	2	19	2	19	4.2%	1.00 [0.16, 6.38]	1993
Chuntrasakul 1996	1	21	3	17	3.1%	0.27 [0.03, 2.37]	1996
Singh 1998	4	21	4	22	9.3%	1.05 [0.30, 3.66]	1998
Minard 2000	1	12	4	15	3.4%	0.31 [0.04, 2.44]	2000
Pupelis 2001	1	30	7	30	3.5%	0.14 [0.02, 1.09]	2001
Malhotra 2004	12	100	16	100	30.1%	0.75 [0.37, 1.50]	2004
Peck 2004	4	14	5	13	12.5%	0.74 [0.25, 2.18]	2004
Nguyen 2008	6	14	6	14	19.9%	1.00 [0.43, 2.35]	2008
Moses 2009	3	29	3	30	6.3%	1.03 [0.23, 4.71]	2009
Chourdakis 2012	3	34	2	25	5.0%	1.10 [0.20, 6.12]	2012
Total (95% CI)		**336**		**326**	**100.0%**	**0.76 [0.52, 1.11]**	
Total events	38		54				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.61$, df = 10 (P = 0.85); $I^2 = 0\%$
Test for overall effect: Z = 1.44 (P = 0.15)

Risk Ratio M-H, Random, 95% CI
0.02 0.1 1 10 50
Favours EEN Favours DEN

Early EN vs. Delayed EN

b Infections

Study or Subgroup	EEN Events	EEN Total	DEN Events	DEN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moore 1986	3	32	9	31	6.4%	0.32 [0.10, 1.08]	1986
Chiarelli 1990	3	10	7	10	8.3%	0.43 [0.15, 1.20]	1990
Eyer 1993	8	19	4	19	8.4%	2.00 [0.72, 5.53]	1993
Hasse 1995	3	14	8	17	7.2%	0.46 [0.15, 1.40]	1995
Watters 1997	1	13	4	15	2.5%	0.29 [0.04, 2.27]	1997
Singh 1998	3	21	8	22	6.6%	0.39 [0.12, 1.28]	1998
Minard 2000	6	12	7	15	12.4%	1.07 [0.49, 2.34]	2000
Pupelis 2001	1	30	8	30	2.6%	0.13 [0.02, 0.94]	2001
Malhotra 2004	21	100	30	100	21.3%	0.70 [0.43, 1.14]	2004
Nguyen 2008	3	14	6	14	6.7%	0.50 [0.15, 1.61]	2008
Chourdakis 2012	13	34	12	25	17.5%	0.80 [0.44, 1.44]	2012
Total (95% CI)		**299**		**298**	**100.0%**	**0.64 [0.46, 0.90]**	
Total events	65		103				

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 13.41$, df = 10 (P = 0.20); $I^2 = 25\%$
Test for overall effect: Z = 2.58 (P = 0.010)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours EEN Favours DEN

Fig. 2 Forest plots (**a** mortality; **b** infections) Question 1B: early EN (EEN) vs. delayed EN (DEN) in unselected critically ill patients

Reintam A, Van Zanten AR et al. Intensive Care Med. 2017 Mar;43(3):380-398

Recommendations (24)

- 17 recommendations favouring initiation of EEN.
- 7 recommendations favouring delaying EN.
- EEN reduced infectious complications in unselected critically ill patients, in patients with severe acute pancreatitis, and after GI surgery.
- We did not detect any evidence of superiority for early PN or delayed EN over EEN.
- All recommendations are weak because of the low quality of evidence, with several based only on expert opinion.

Reintam A, Van Zanten AR et al. Intensive Care Med. 2017 Mar;43(3):380-398

Early Enteral Nutrition is safe and recommended:

- <u>In controlled shock</u>
- When using NMBA
- Targeted Temperature Management
- ECMO
- Prone position
- TBI, stroke, spinal cord injury
- Severe acute Pancreatitis
- GI surgery

- Abdominal aortic surgery
- Abdominal trauma
- Open abdomen
- Intra-abdominal Hypertension without compartment syndrome
- Liver failure (independent of grade of encephalopathy)
- Absent bowel sounds
- Diarrhea

Reintam A, Van Zanten AR, et al. Intensive Care Med. 2017, 43: 380–398.

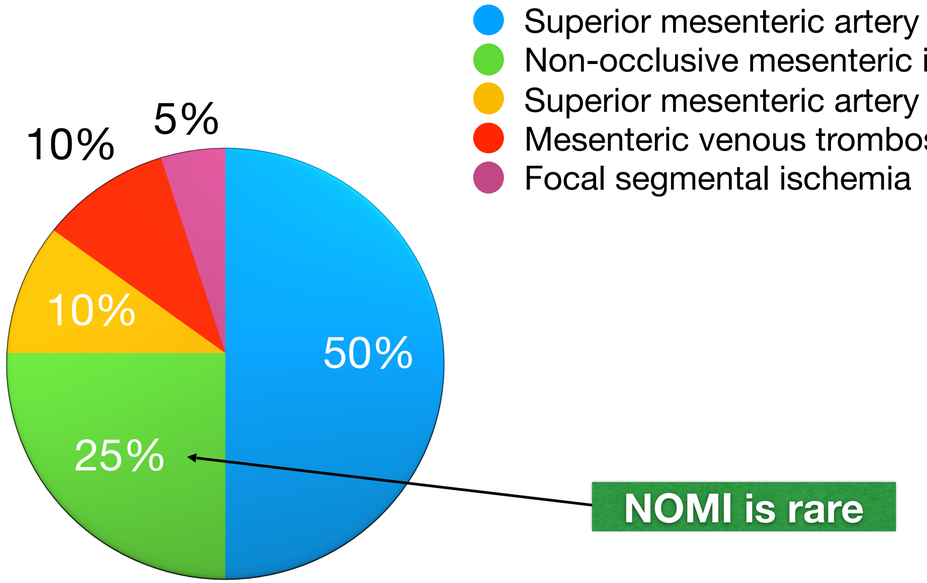
When to delay enteral nutrition?

- In bowel obstruction (not post-operative ileus)
- In uncontrolled shock
- Overt bowel ischemia
- High-output fistula that cannot be bypassed
- In abdominal compartment syndrome, when during IAH and EEN abdominal pressure increases
- Active GI-bleeding
- GRV>500 mL/6h

Reintam A, Van Zanten AR, et al. Intensive Care Med. 2017, 43: 380–398.

Always resuscitate patient before starting EEN

- **Fluid therapy**
- **Vasopressor start**
- **Stable MAP (>65 mmHg)**
- **Acceptable $ScVO_2$ (65-70%)**
- **Acceptable lactate < 2.5 mmol/l or 50% drop**
- **Most patients are stable within 6-12 hours**
- **Then start EEN (<24h)**



We did not encounter 1 single case of non-occlusive mesenteric ischemia due to EN in >1000 ICU patients using this checklist

ESPEN ICU guidelines 2018

- **Recommendation 38: EN should be delayed:**

  - If shock is uncontrolled and hemodynamic and tissue perfusion goals are not reached, whereas low dose EN can be started as soon as shock is controlled with fluids and vasopressors/inotropes, while remaining vigilant for signs of bowel ischemia;

  - In case of uncontrolled life-threatening hypoxemia, hypercapnia or acidosis, whereas EN can be started in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis;

  - In patients suffering from active upper GI bleeding, whereas EN can be started when the bleeding has stopped and no signs of re-bleeding are observed;

  - In patients with overt bowel ischemia;

  - In patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable;

  - In patients with abdominal compartment syndrome; and

  - If gastric aspirate volume is above 500 ml/6h.

  Grade of recommendation: B – strong consensus (100 % agreement)

ESPEN ICU guidelines 2018

Recommendation 39: Low dose EN should be administered

- In patients receiving therapeutic hypothermia and increasing the dose after rewarming;

- In patients with intra-abdominal hypertension without abdominal compartment syndrome, whereas temporary reduction or discontinuation of EN should be considered when intra-abdominal pressure values further increase under EN; and

- In patients with acute liver failure when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy. Grade of recommendation: B – strong consensus (95.65 % agreement)

Conclusies

- Early EN > Delayed EN > Delayed PN > Early PN
- First resuscitate the gut
- Biomarker: No, clinical judgement or CT-angio
- EEN in abdominal hypertension yes, in abdominal compartment syndrome no
- 7 reasons to delay EN: uncontrolled shock
- Most patients HD stabile after 6-12 hours
- Median in Ede 5.6 hours

Definition

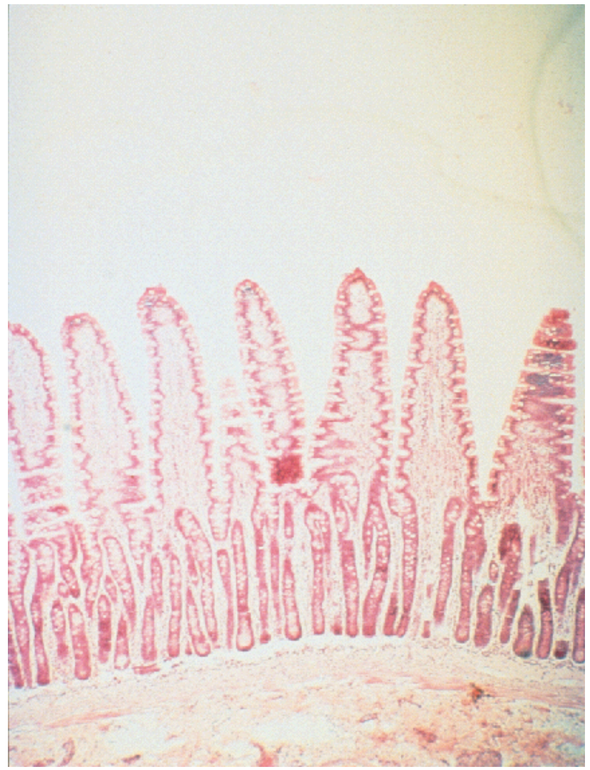
- **Early Enteral Nutrition (EEN):**
- **Enteral nutrition is initiated within 24 – 48 hours following hospitalization, trauma, or injury**

For ICU patients after admission to ICU

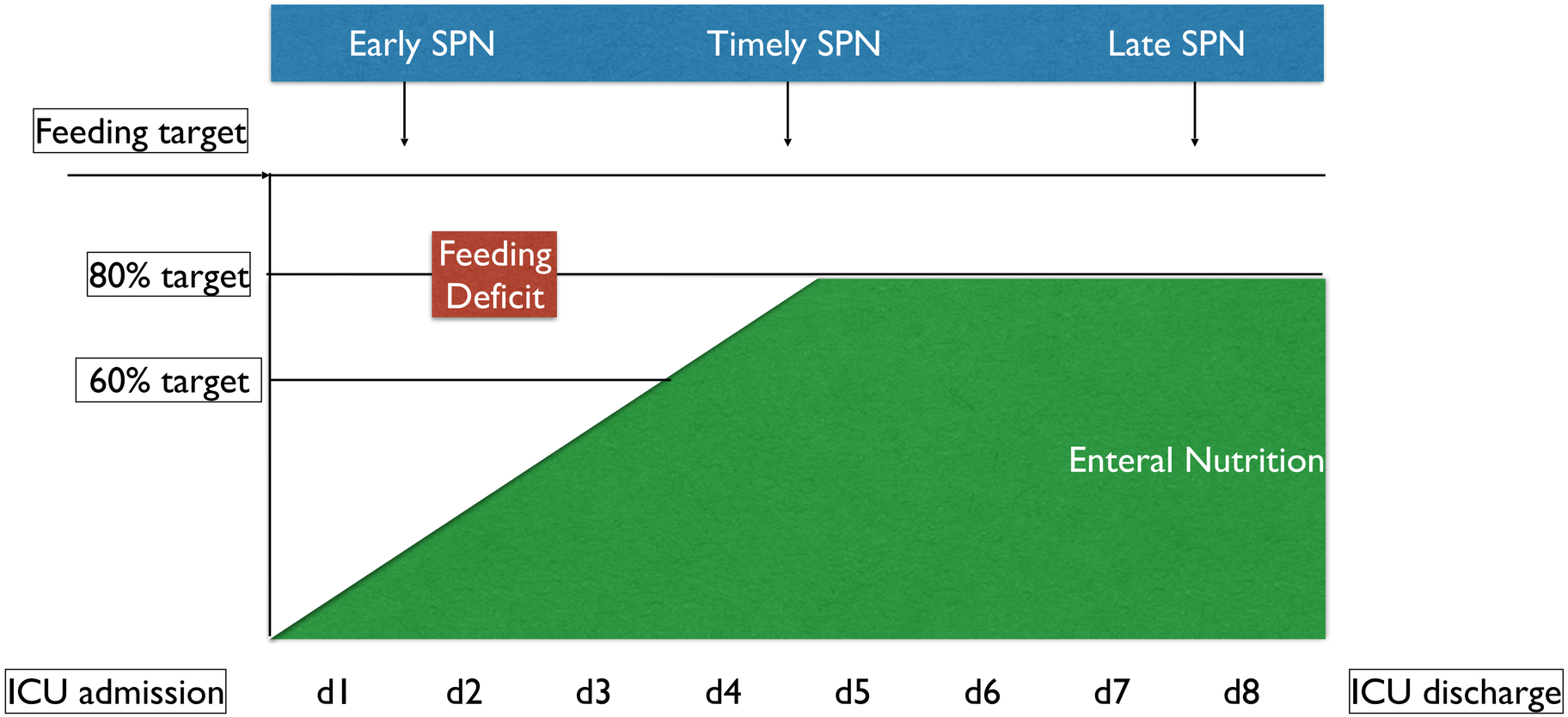
Zaloga GP. Crit Care Med 1999;27:259
Alverdy Crit Care Med 2003;31:598

Why EEN?

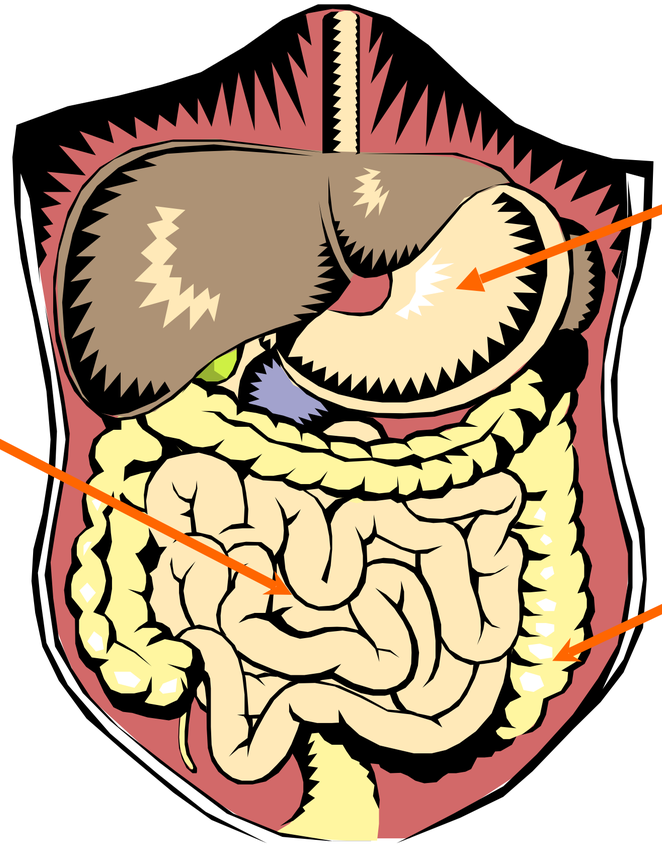
- To maintain intestinal mucosal integrity
  - Normal microvilli
  - Height and number
  - Normal intestinal barrier
  - Intestinal mucosal immunity
- Provide nutrients required during metabolic stress
- Reduce morbidity compared with parenteral nutrition
- Reduce cost compared with parenteral nutrition



Enteral Nutrition



Usual Postoperative Organ Recovery Times



Stomach
24–48 hr

Small Intestine
12–24 hr

Large Intestine
48–120 hr

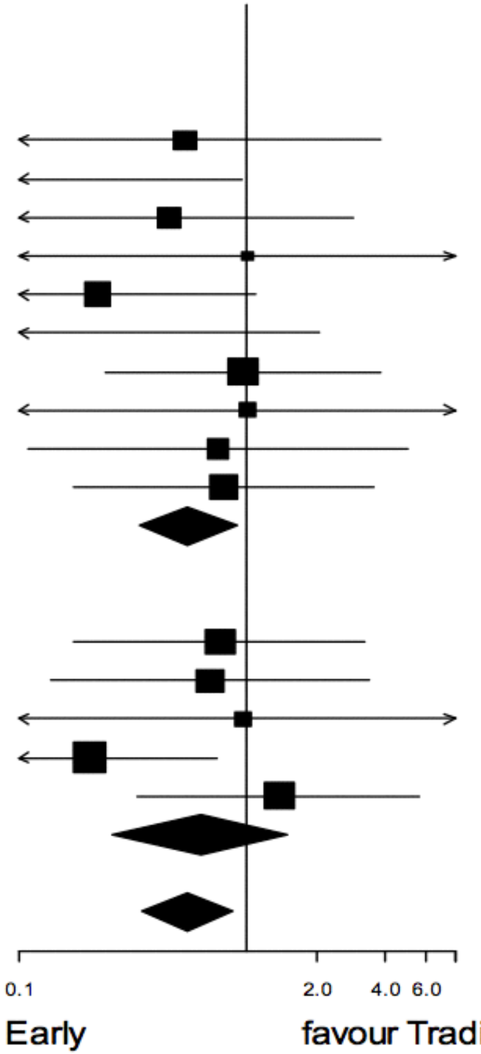
Do Not Wait for Bowel Sounds

electromyographic activity

Luckey A, et al. Arch Surg. 2003;138:206-214.
Livingston EH, Passaro EP Jr. Dig Dis Sci. 1990;35:121-132.
Delaney CP, et al. Clinical Consensus Update in General Surgery. 2006.

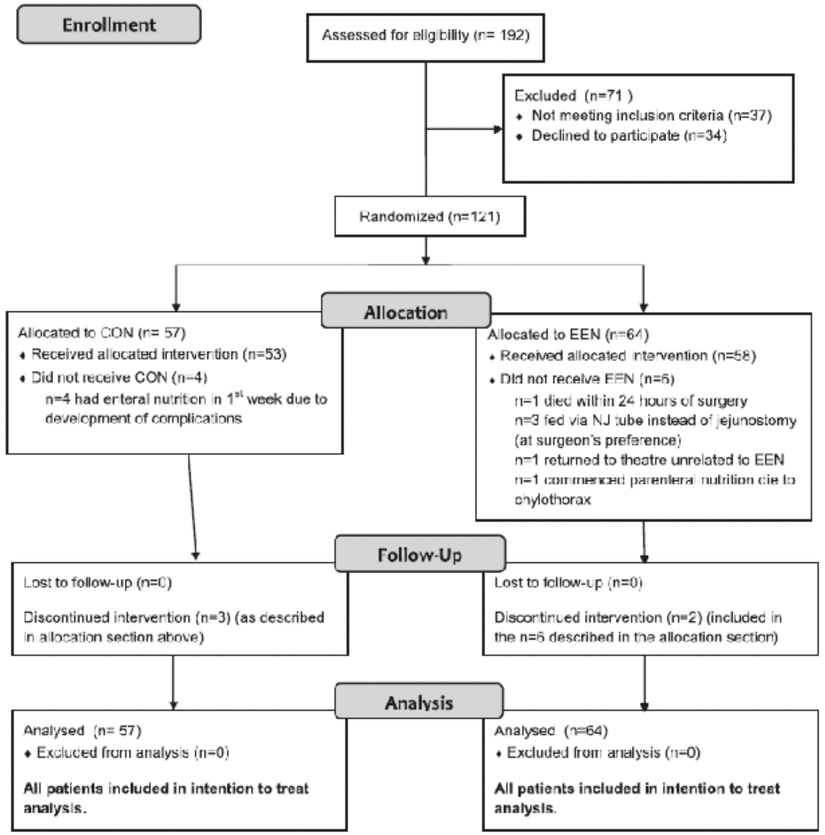
Less Postoperative Complications in EEN

Study	Early	Traditional	OR	L	U
pre 2000					
Sagar	3 of 15	5 of 15	0.53	0.08	3.78
Ryan	2 of 7	7 of 7	0.03	0	0.94
Schroeder	4 of 16	7 of 16	0.46	0.07	2.91
Binderow	0 of 32	0 of 32	1	0.02	61.41
Beier-Holgersen	8 of 30	19 of 30	0.22	0.05	1.08
Carr	0 of 14	4 of 14	0.08	0	2.06
Ortiz	17 of 93	18 of 95	0.96	0.24	3.77
Hartsell	1 of 29	1 of 29	1	0.07	13.42
Nessim	3 of 27	4 of 27	0.75	0.11	5.01
Stewart	10 of 40	12 of 40	0.78	0.17	3.56
subtotal	**48 of 303**	**77 of 305**	**0.55**	**0.34**	**0.9**
post 2000					
Han-Geurts	12 of 56	13 of 49	0.76	0.18	3.27
Delaney	7 of 31	10 of 33	0.69	0.14	3.38
Lucha	1 of 26	1 of 25	0.96	0.07	12.99
Zhou	23 of 161	70 of 155	0.21	0.06	0.74
Han-Geurts	22 of 46	20 of 50	1.37	0.33	5.61
subtotal	**65 of 320**	**114 of 312**	**0.62**	**0.26**	**1.51**
POOLED	**113 of 623**	**191 of 617**	**0.55**	**0.35**	**0.87**



Osland et al. JPEN 2011

RCT EEN in patients undergoing major upper gastrointestinal resection



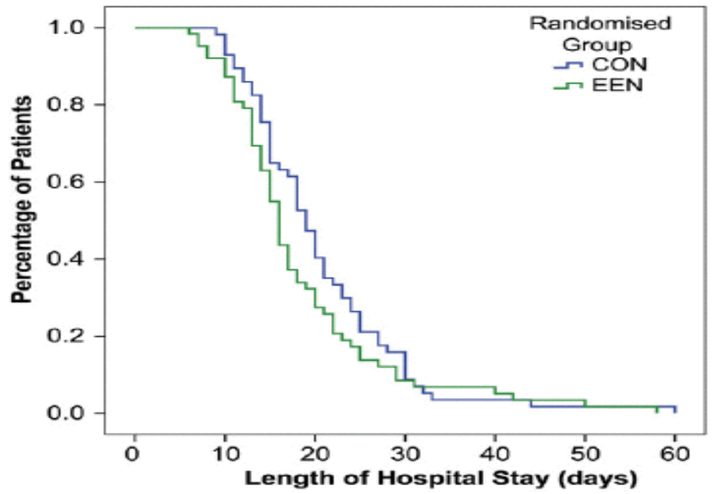


Fig. 2. Duration of hospital stay related to randomisation.

Median Hospital LOS
16 days vs. 19 days (p=0.023)

Barlow R, et al. ClinNutr,2011;30:560-566.

RCT EEN in patients undergoing major upper gastrointestinal resection

Complication	Conventional	Early EN	P-value
Infective Complications			
Wound infection	16 (28.1)	7 (10.9)	0.017
Chest infection	12 (21.1)	5 (7.8)	0.036
Anastomotic leakage	7 (12.2)	2 (3.1)	0.055
UTI	3 (5.3)	1 (1.6)	
Bacteraemia	3 (5.3)	2 (3.1)	
Non-infective complications			
Pleural effusion	10 (17.5)	10 (15.6)	
Delayed gastric emptying	4 (7.0)	0	0.031
Myocardial infarction	1 (1.8)	0	
Major haemorrhage	2 (3.5)	0	
Chylothorax	0	1 (1.6)	
Rec. Laryngeal nerve palsy	0	1 (1.6)	

Barlow R, et al. ClinNutr,2011;30:560-566.

EN better effect than TPN on gut barrier function in severe acute pancreatitis

	Enteral nutrition N= 29	Parenteral nutrition N=34	P-value
Endotoxin (EU/l)			
Day 07	39.30 ± 15.82	73.05 ± 21.16	P < 0.05
Day 14	22.64 ± 14.31	49.34 ± 24.54	P < 0.05
Day 21	14.81 ± 10.93	30.08 ± 14.10	P < 0.05
Lactulose: mannitol ratio (urine)			
Day 07	0.28 ± 0.25	0.65 ± 0.45	P < 0.05
Day 14	0.21 ± 0.18	0.54 ± 0.41	P < 0.05
Day 21	0.08 ± 0.04	0.29 ± 0.06	P < 0.05

EN Less endotoxinemia and better gut integrity

Xu CF Zhonghua Nei Ke Za Zhi. 2011;50(5):370-3

Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients

impact of delayed enteral nutrition on small intestinal absorption of 3-O-methyl-glucose:
Gastric emptying (scintigraphy) similar

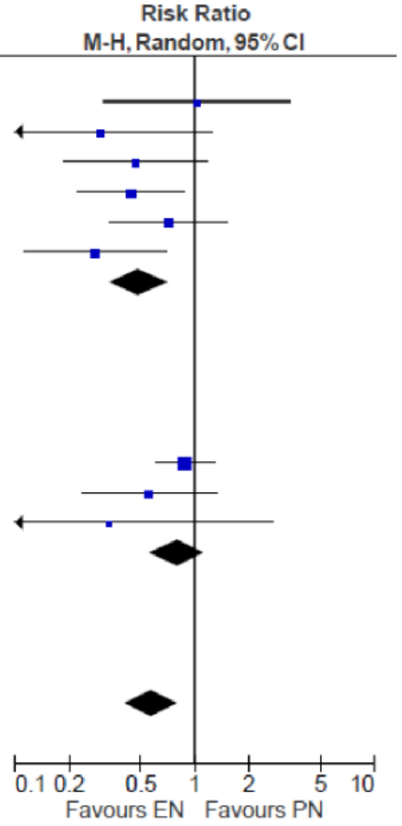
	Enteral nutrition < 24 hours N= 14	Enteral nutrition > 4 days N=14	P-value
3-O-methyl-glucose day 4			
Peak	0.37 ± 0.04	0.24 ± 0.04	P < 0.02
AUC 240 min	63.4 ± 8.3	38.5 ± 7.0	P < 0.04
Mechanical ventilation			
Days	9.2 ± 0.9	13.7 ± 1.9	P < 0.05
ICU length of stay			
Days	11.3 ± 0.8	15.9 ± 1.9	P < 0.05

Delaying enteral feeding is associated with a reduction in small intestinal glucose absorption
These observations support recommendations for "early" enteral nutrition in critically ill patients

Nguyen N. Crit Care Med. 2012;40(1):50-4

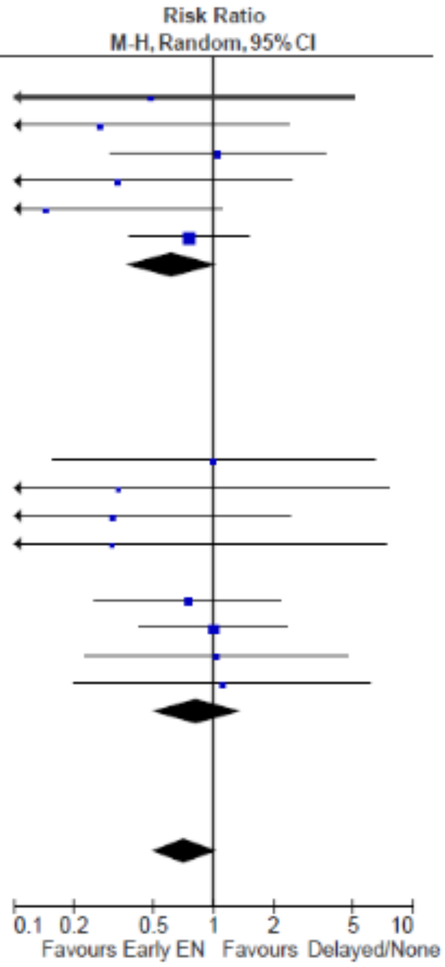
EN Less infections compared to PN

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Infections (PN>EN kcal)							
Young	5	28	4	23	6.6%	1.03 [0.31, 3.39]	1987
Peterson	2	21	8	25	4.8%	0.30 [0.07, 1.25]	1988
Moore	5	29	11	30	9.9%	0.47 [0.19, 1.19]	1989
Kudsk	9	51	18	45	14.9%	0.44 [0.22, 0.88]	1992
Woodcock	6	16	11	21	13.4%	0.72 [0.34, 1.52]	2001
Chen	5	49	18	49	10.2%	0.28 [0.11, 0.69]	2011
Subtotal (95% CI)		**194**		**193**	**59.8%**	**0.49 [0.34, 0.71]**	
Total events	32		70				
Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 5 (P = 0.47); I² = 0%							
Test for overall effect: Z = 3.81 (P = 0.0001)							
1.1.2 Infections (PN~EN kcal)							
Adams	15	23	17	23	26.8%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	11.0%	0.56 [0.23, 1.32]	1997
Casas	1	11	3	11	2.4%	0.33 [0.04, 2.73]	2007
Subtotal (95% CI)		**52**		**54**	**40.2%**	**0.80 [0.56, 1.13]**	
Total events	21		30				
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 2 (P = 0.38); I² = 0%							
Test for overall effect: Z = 1.28 (P = 0.20)							
Total (95% CI)		**246**		**247**	**100.0%**	**0.58 [0.41, 0.80]**	
Total events	53		100				
Heterogeneity: Tau² = 0.07; Chi² = 11.24, df = 8 (P = 0.19); I² = 29%							
Test for overall effect: Z = 3.24 (P = 0.001)							
Test for subgroup differences: Chi² = 3.59, df = 1 (P = 0.06), I² = 72.2%							



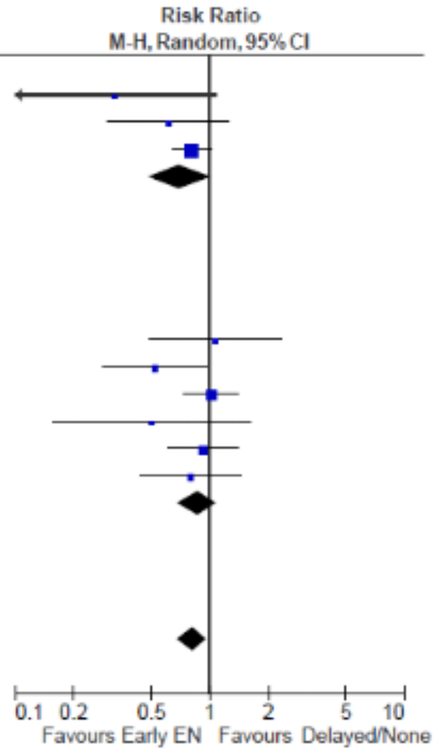
EEN trend to lower mortality

Study or Subgroup	Early EN Events	Total	Delayed/None Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 EN vs IV Fluids/No 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: Tau² = 0.00; Chi² = 4.10, df = 5 (P = 0.54); I² = 0%							
Test for overall effect: Z = 1.78 (P = 0.08)							
1.1.2 EN vs Delayed EN							
Chiarelli	0	10	0	10		Not estimable	1990
Eyer	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: Tau² = 0.00; Chi² = 2.07, df = 7 (P = 0.96); I² = 0%							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)		395		393	100.0%	0.72 [0.50, 1.04]	
Total events	39		61				
Heterogeneity: Tau² = 0.00; Chi² = 6.83, df = 13 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.76 (P = 0.08)							
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.44), I² = 0%							



EEN less infections

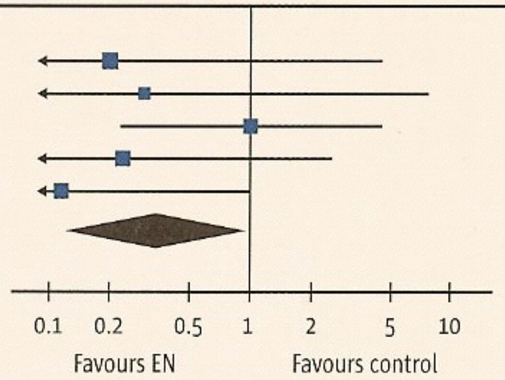
Study or Subgroup	Early EN Events	Total	Delayed/None Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 EN vs IV Fluids/No EN							
Moore	3	32	9	31	2.0%	0.32 [0.10, 1.08]	1986
Singh	7	21	12	22	5.5%	0.61 [0.30, 1.25]	1998
Malhotra	54	100	67	100	33.8%	0.81 [0.64, 1.01]	2004
Subtotal (95% CI)		**153**		**153**	**41.3%**	**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)							
1.2.2 EN vs Delayed EN							
Minard	6	12	7	15	4.6%	1.07 [0.49, 2.34]	2000
Kompan 2004	9	27	16	25	7.4%	0.52 [0.28, 0.96]	2004
Peck	12	14	11	13	22.0%	1.01 [0.74, 1.39]	2004
Nguyen 2008	3	14	6	14	2.1%	0.50 [0.15, 1.61]	2008
Moses	17	29	19	30	14.7%	0.93 [0.61, 1.39]	2009
Chourdakis	13	34	12	25	7.8%	0.80 [0.44, 1.44]	2012
Subtotal (95% CI)		**130**		**122**	**58.7%**	**0.86 [0.69, 1.08]**	
Total events	60		71				
Heterogeneity: Tau² = 0.01; Chi² = 5.71, df = 5 (P = 0.34); I² = 12%							
Test for overall effect: Z = 1.27 (P = 0.20)							
Total (95% CI)		283		275	100.0%	0.81 [0.68, 0.97]	
Total events	124		159				
Heterogeneity: Tau² = 0.01; Chi² = 9.30, df = 8 (P = 0.32); I² = 14%							
Test for overall effect: Z = 2.35 (P = 0.02)							
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%							



Early EN (<24h) vs. Control

Mortality

Study or sub-category	Early EN (<24 h) n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Chiarelli 1990	0/10	0/10			Not estimable
Kompan 1999	0/17	2/19		13.40	0.20 [0.01, 4.47]
Kompan 2004	0/27	1/25		8.89	0.30 [0.01, 7.63]
Nguyen 2008	6/14	6/14		19.95	1.00 [0.22, 4.47]
Chuntrasakul 1996	1/21	3/17		18.38	0.23 [0.02, 2.48]
Pupelis 2001	1/30	7/30		39.38	0.11 [0.01, 0.99]
Total (95% CI)	**119**	**115**		**100**	**0.34 [0.14, 0.85]**
Total events: 8 (early EN (<24 h)), 19 (Control)					
Test for heterogeneity: $Chi^2 = 3.20$, df = 4 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.31 (P = 0.02)					



Early enteral nutrition lower mortality
Odds ratio 0.34 (0.14-0.85)
Numbers needed to treat: 11 to prevent one death

Very Early enteral nutrition is best

Doig G. Intensive Care Med 2009;35:2018-27

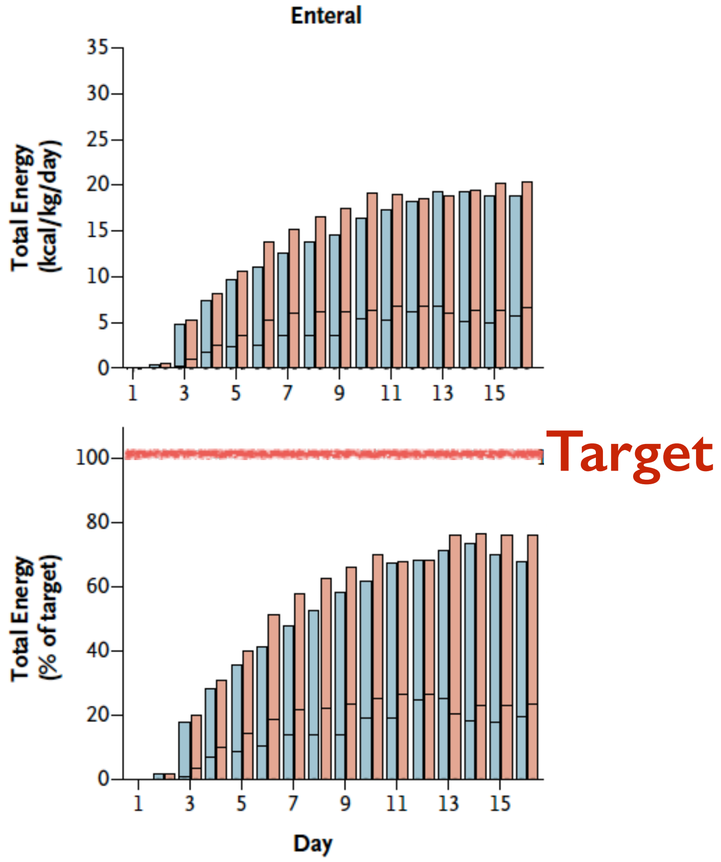
Energy overfeeding is harmful

N=843	OR	95% CI	P-value
Daily protein intake groups [a]	0.85	0.73-0.99	0.047
Energy overfeeding (y/n) [b]	1.62	1.07-2.44	0.022
Sepsis (y/n)	1.77	1.18-2.65	0.005
APACHE-II score	1.04	1.02-1.05	<0.001

[a] Protein intake groups were <0.8, 0.8 - <1.0, 1.0 - <1.2, and ≥1.2 g/kg.
[b] day 4 energy overfeeding was defined as an energy intake of more than 110% of measured energy expenditure

Weijs P. Crit Care 2014;18:701

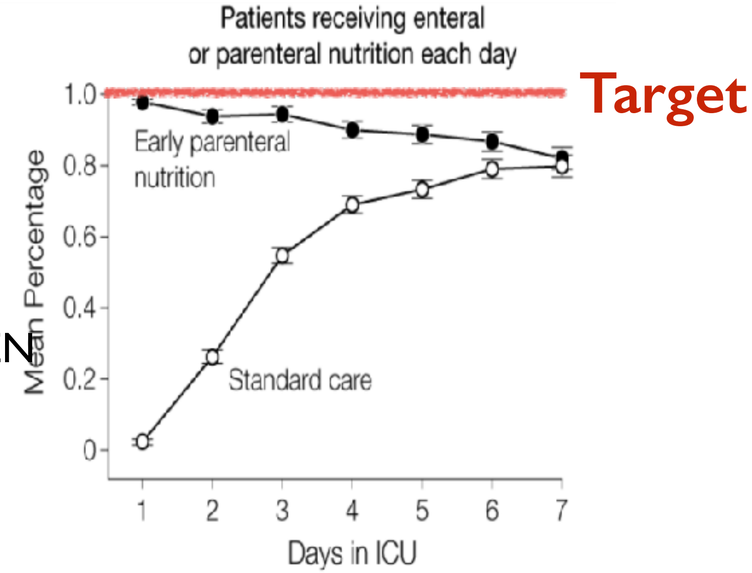
Relevant in EN?



No. in ICU						
Late initiation	2328	1399	913	655	436	313
Early initiation	2312	1438	975	736	517	371

Epanic trial n= 4640

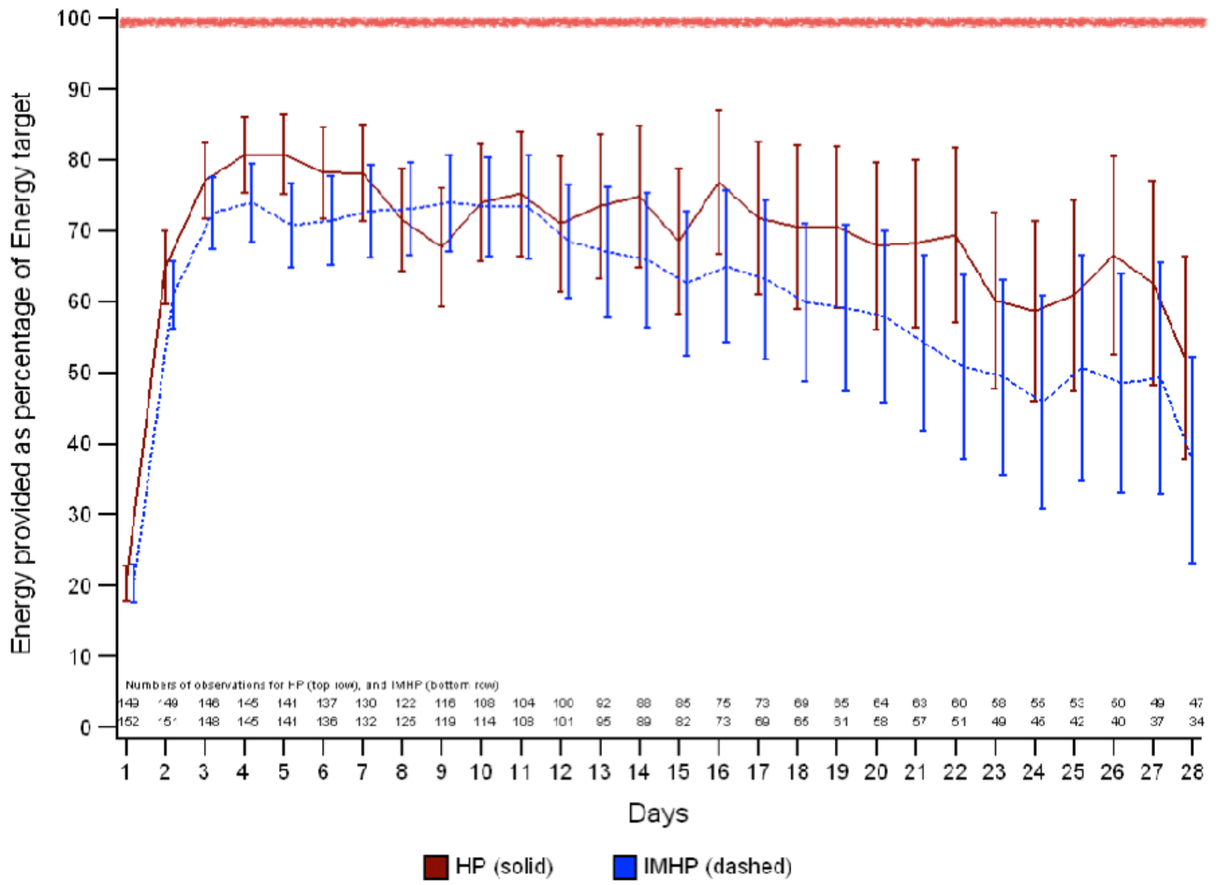
EN



No. of patients							
Early parenteral nutrition	681	676	611	518	435	376	313
Standard care	682	675	599	480	410	353	301

Early PN trial n = 1363

Mean Energy intake in the MetaPlus trial n= 301



Target

Means (95% CI) from day 1 until day 28.

All ITT analysis patients were included.

Energy targets were calculated as follows: 25 kcal/kg body weight * day, with a maximum of 2500 kcal/day.

intake from study products as percentage of calculated energy target during ICU stay

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

ESPEN ICU guidelines 2018

- **Recommendation 3: Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.**

- **Grade of recommendation: GPP – strong consensus (100 % agreement)**

- **Recommendation 4 : If oral intake is not possible, early EN (within 48 hours) in critically ill adult patients should be performed/initiated rather than delaying EN.**

- **Grade of recommendation: B – strong consensus (100 % agreement)**

- **Recommendation 5: If oral intake is not possible, early EN (within 48 hours) shall be performed/initiated in critically ill adult patients rather than early PN.**

- **Grade of recommendation: A – strong consensus (100 % agreement)**

CRITICAL CARE NUTRITION ACADEMY

Ziekenhuis Gelderse Vallei

Conclusions

- EN is first line therapy in ICU patients
- No risk of overfeeding
- EN is essential and trophic for the gut, the microbiota
- Probably non-nutritional aspects more important
- Trend to mortality reduction, less infections