Early enteral nutrition in ICU patients:
Is 48 h early enough?

Dr. Gordon S. Doig
Associate Professor in Intensive Care
Northern Clinical School Intensive Care Research Unit,
University of Sydney, Sydney, Australia
www.EvidenceBased.net
gdoig@med.usyd.edu.au

A pdf version of this talk can be downloaded from the Talks section of our outreach education web site (www.EvidenceBased.net).

I will show this QR code again at the end of the talk

Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.

Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.

Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.

Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.

Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.

Background: Review of the Guidelines

- 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

Background: Review of the Guidelines

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

Background: Review of the Guidelines

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.
  - *Daren Heyland’s Canadian guideline,*

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Background: Review of the Guidelines

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h – *Daren Heyland’s Canadian guideline,* Trend towards mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Background: Review of the Guidelines

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h
- *Daren Heyland’s Canadian guideline,*
- *European (ESPEN) guideline,*

Trend towards mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.
Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.
Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

Background: Review of the Guidelines

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

< 48 h	– *Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h	– *European (ESPEN) guideline,*	No effect on mortality.
	– *ACCEPT guideline (also Canadian),*	

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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.

Background: Review of the Guidelines

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

< 48 h	– *Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h	– *European (ESPEN) guideline,*	No effect on mortality.
< 24 h	– *ACCEPT guideline (also Canadian),*	Significant mortality reduction.
	– *Australian and New Zealand guideline,*	

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

Background: Review of the Guidelines

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

< 48 h	– *Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h	– *European (ESPEN) guideline,*	No effect on mortality.
< 24 h	– *ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h	– *Australian and New Zealand guideline,*	Significant mortality reduction.
	– *American (SCCM and ASPEN) guideline*	

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

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.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 48 h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

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.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 48 h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

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.

Background: Review of the Guidelines

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 48 h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction.

Heyland DK, *et al*. The 2018 Canadian critical care nutrition guideline. www.CriticalCareNutrition/cpg.

Singer P, Blaser AR, Berger MM *et al*. ESPEN Guidelines on clinical nutrition in the intensive care unit. *Clinical Nutrition* **2019**;38:48-79.

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**.

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.

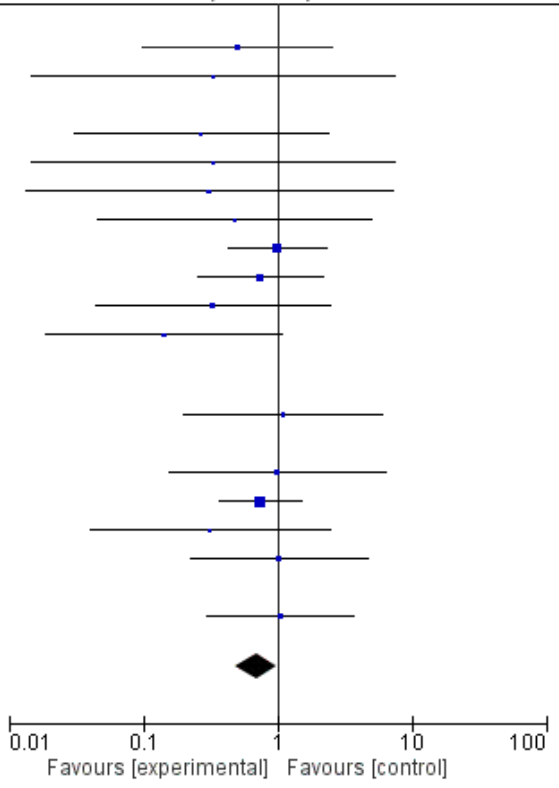
2016 SCCM and ASPEN guideline (eEN < 48h)

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
Chiarelli 1990	0	10	0	10		Not estimable
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
Schroeder 1991	0	16	0	16		Not estimable
Watters 1997	0	13	0	15		Not estimable
Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
Dvorak 2004	0	7	0	10		Not estimable
Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
Sagar 1979	0	15	0	15		Not estimable
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
Total events	41		66			

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%

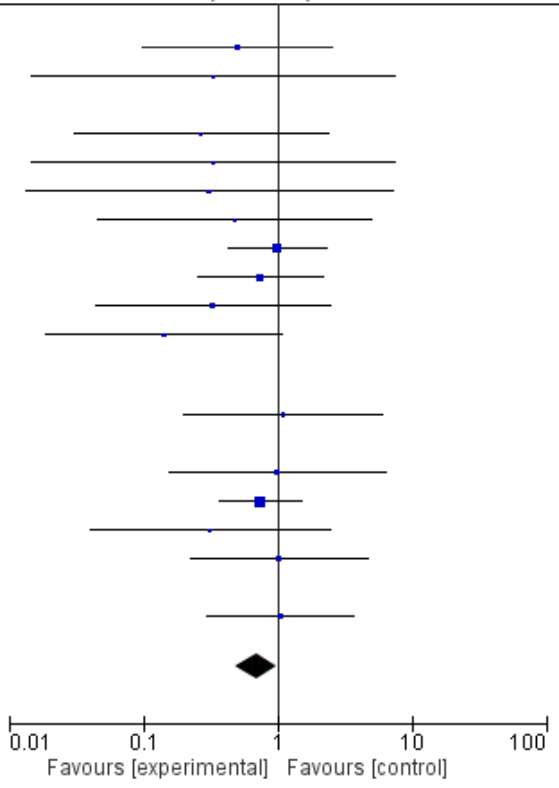


McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
Chiarelli 1990	0	10	0	10		Not estimable
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
Schroeder 1991	0	16	0	16		Not estimable
Watters 1997	0	13	0	15		Not estimable
Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
Dvorak 2004	0	7	0	10		Not estimable
Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
Sagar 1979	0	15	0	15		Not estimable
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
Total events	41		66			

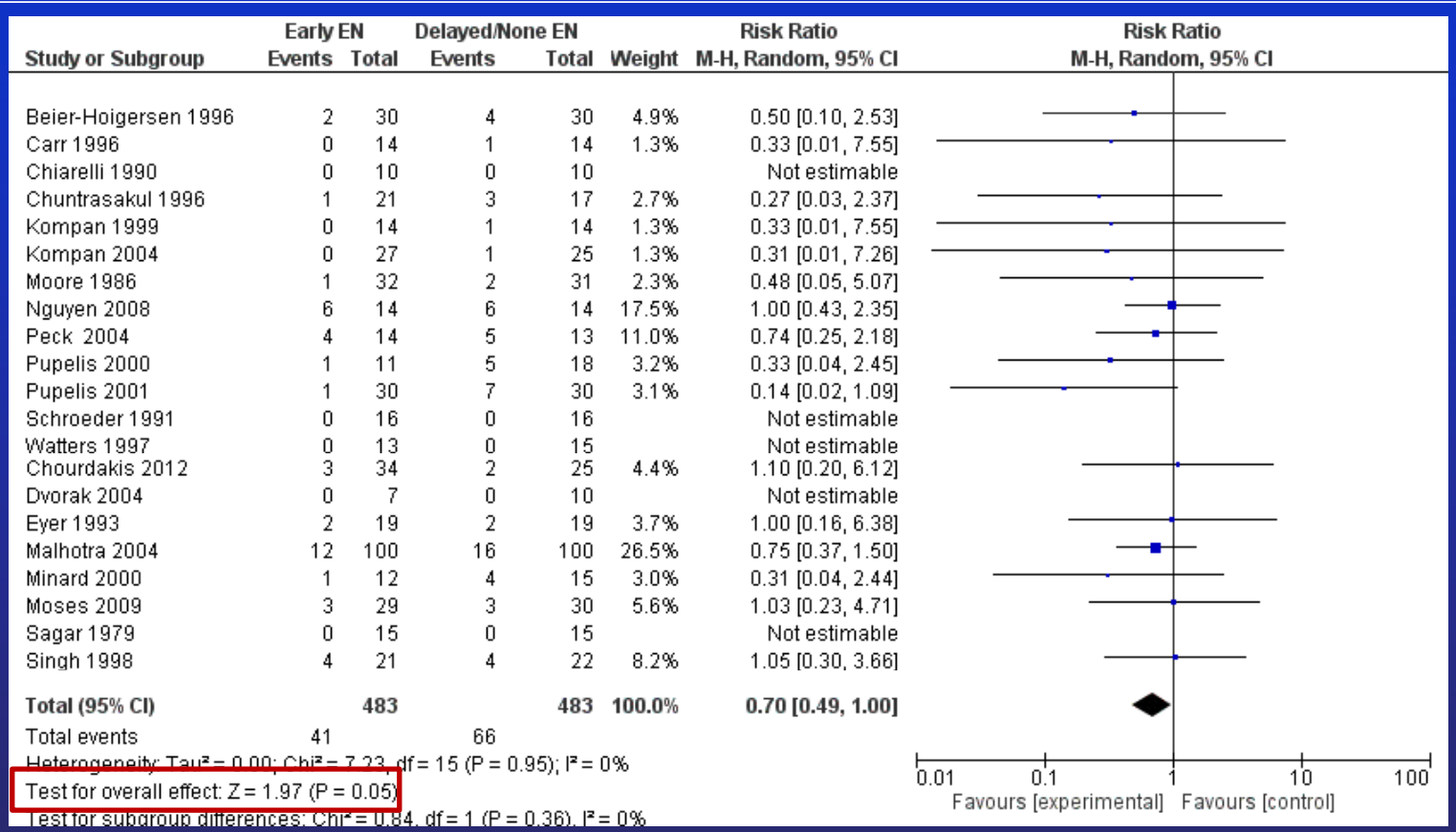
Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%



21 clinical trials

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)



21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

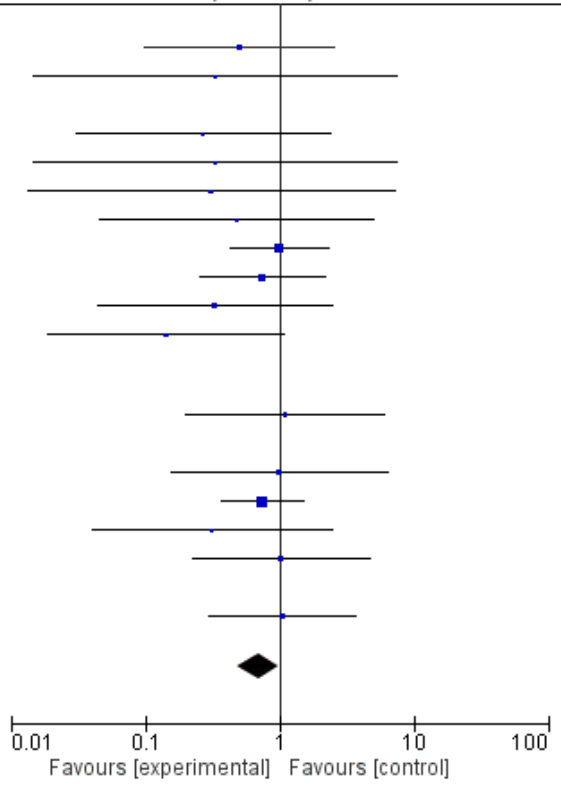
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
	Dvorak 2004	0	7	0	10		Not estimable
	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
	Sagar 1979	0	15	0	15		Not estimable
	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
	Total events	41		66			

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%



21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

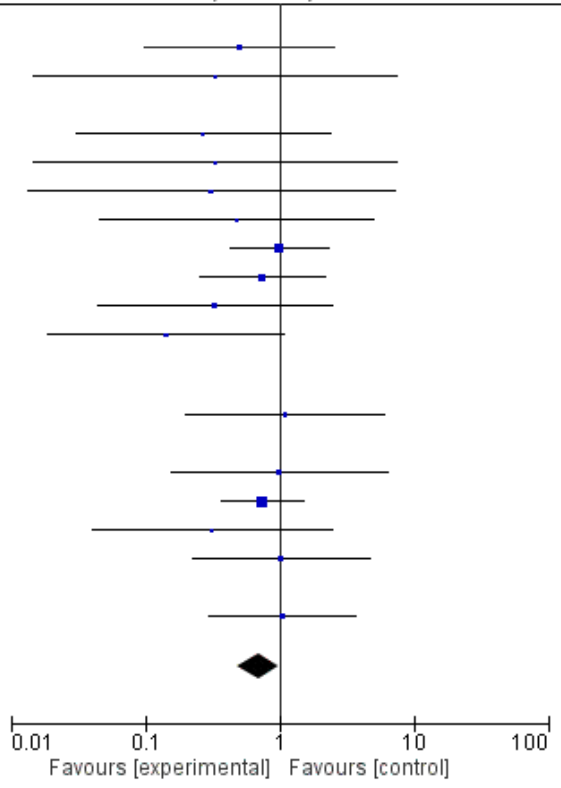
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
	Total events	41		66			

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%



21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

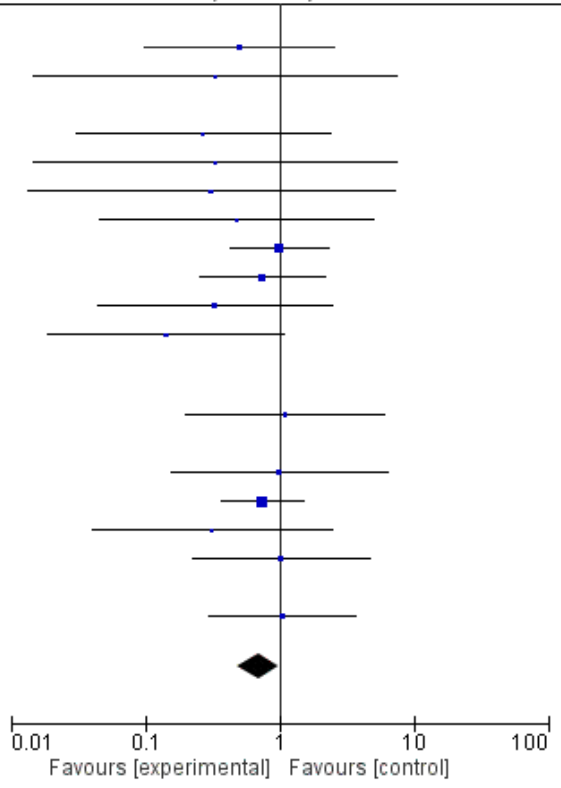
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
	Total events	41		66			

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%



21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

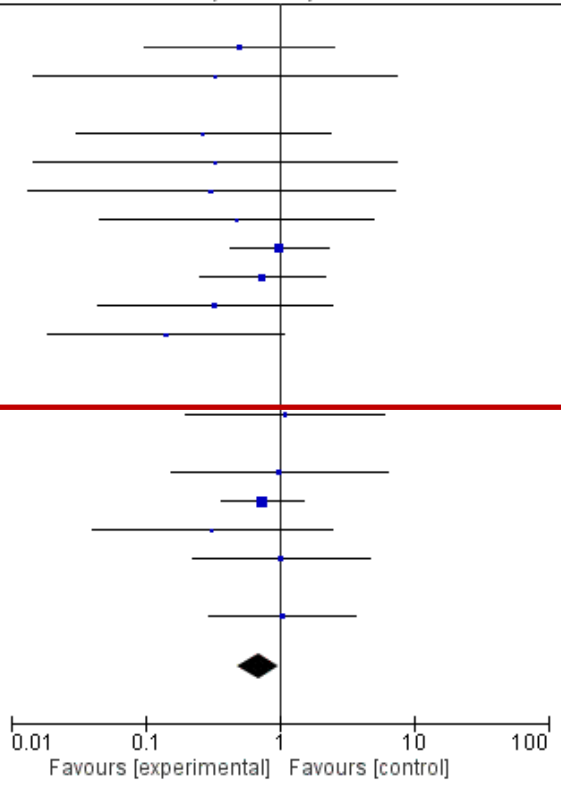
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
	Total events	41		66			

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%



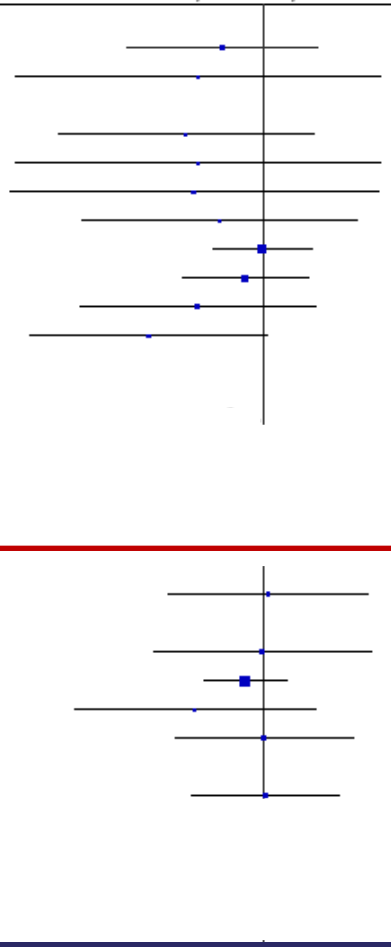
21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

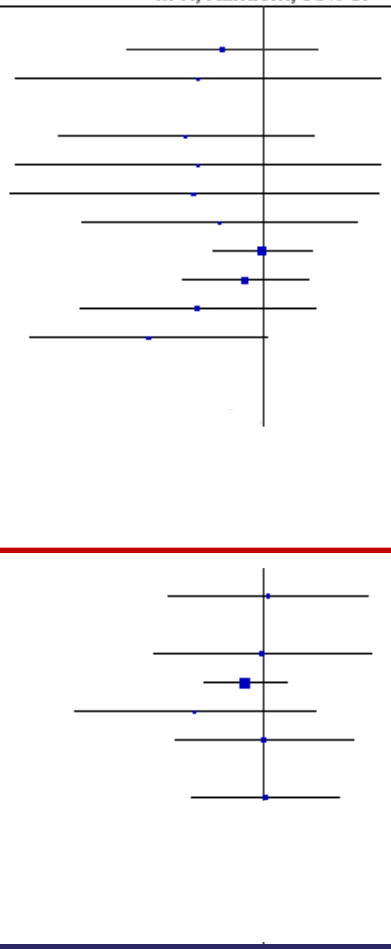
	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

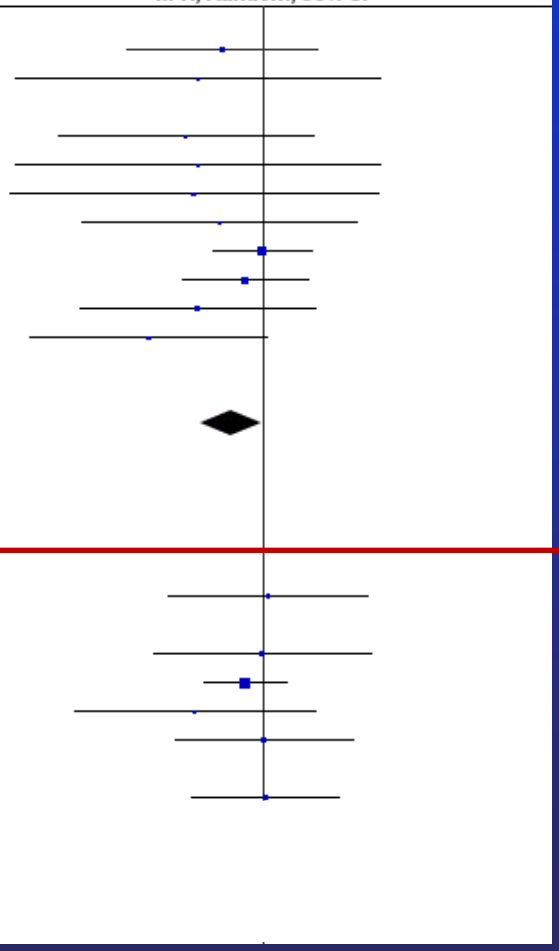
	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

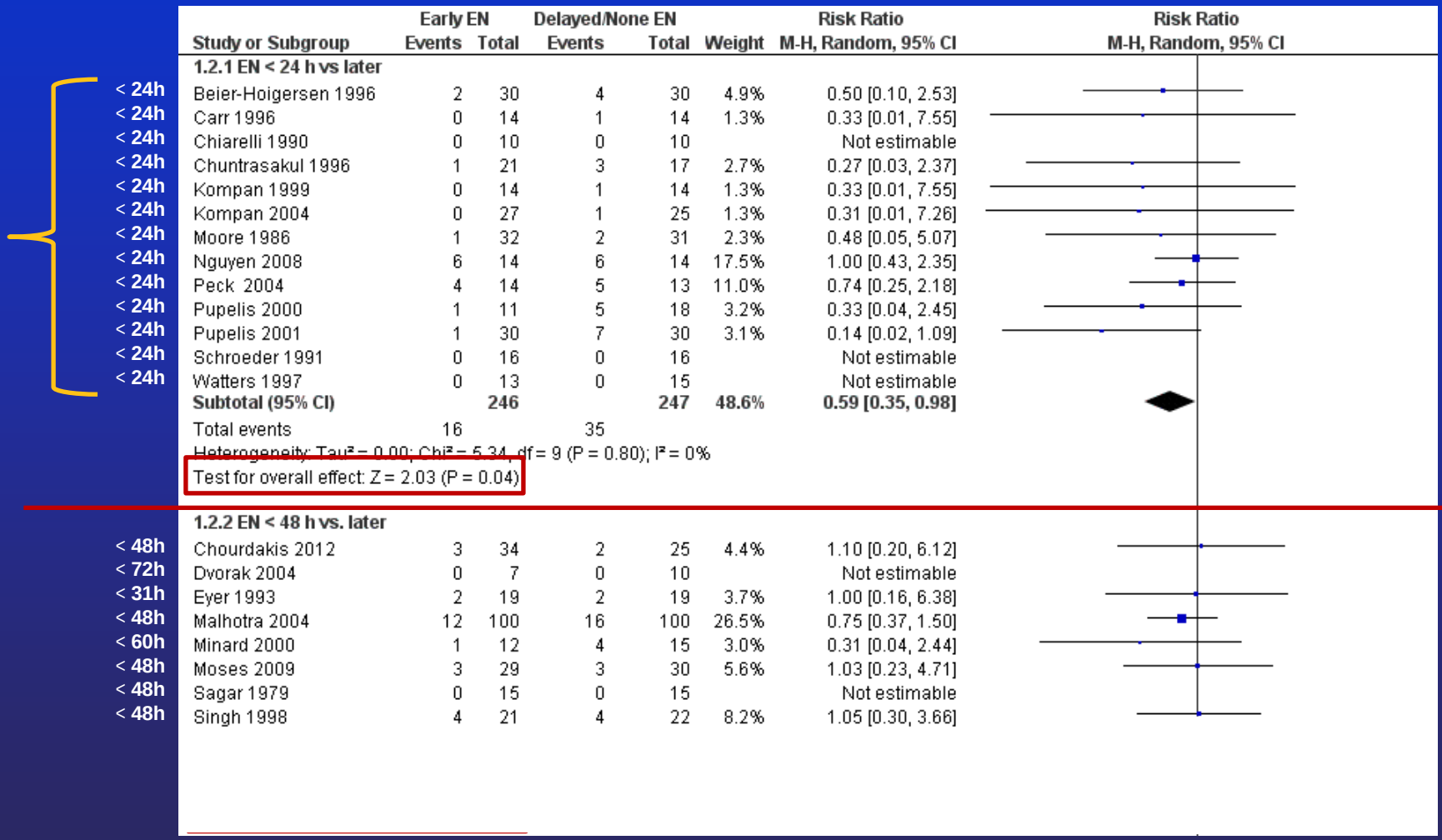
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
	Heterogeneity: Tau² = 0.00; Chi² = 5.34, df = 9 (P = 0.80); I² = 0%						
	Test for overall effect: Z = 2.03 (P = 0.04)						
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

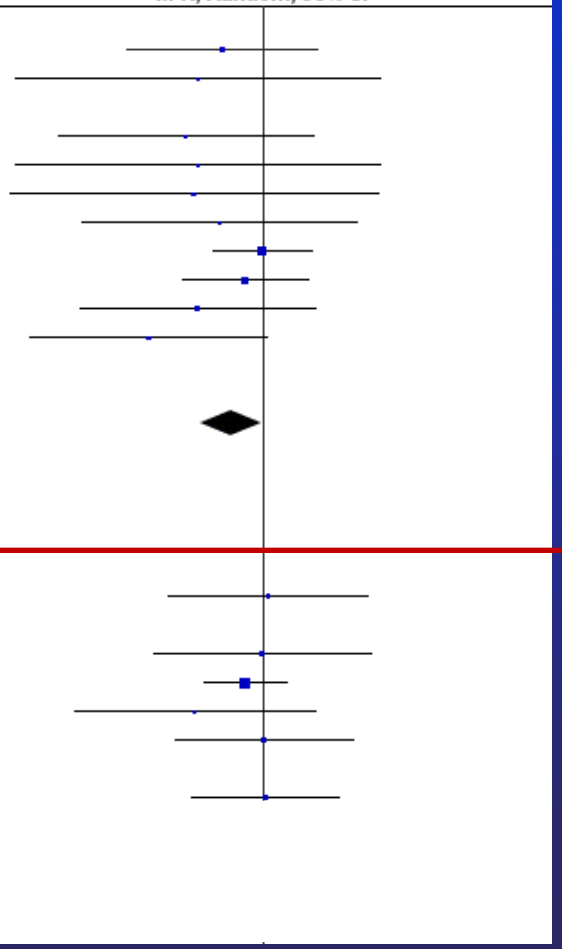


	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.34$, df = 9 (P = 0.80); $I^2 = 0\%$						
	Test for overall effect: Z = 2.03 (P = 0.04)						
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

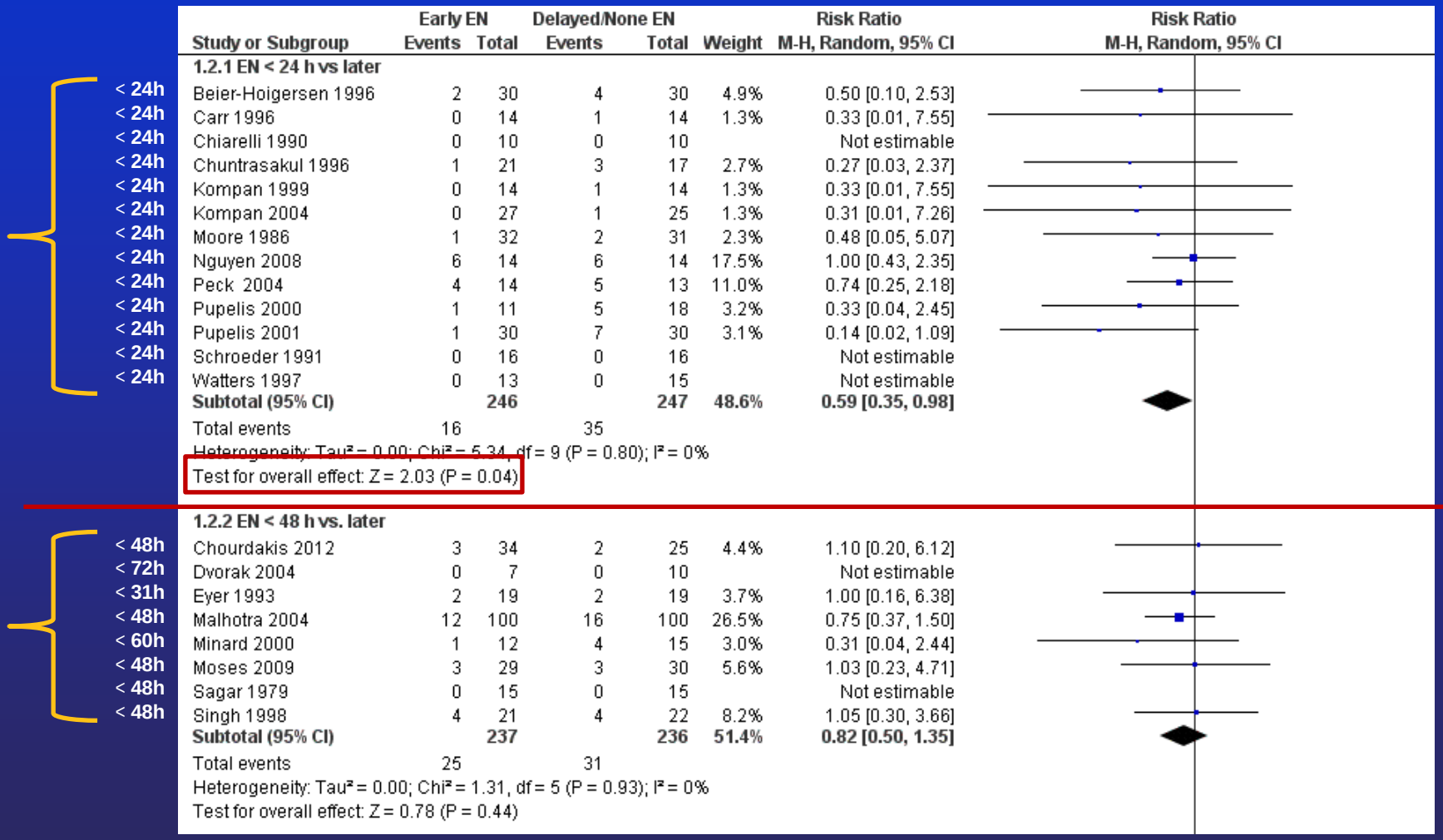
2016 SCCM and ASPEN guideline (eEN < 48h)

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.34$, df = 9 (P = 0.80); $I^2 = 0\%$						
	Test for overall effect: Z = 2.03 (P = 0.04)						
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

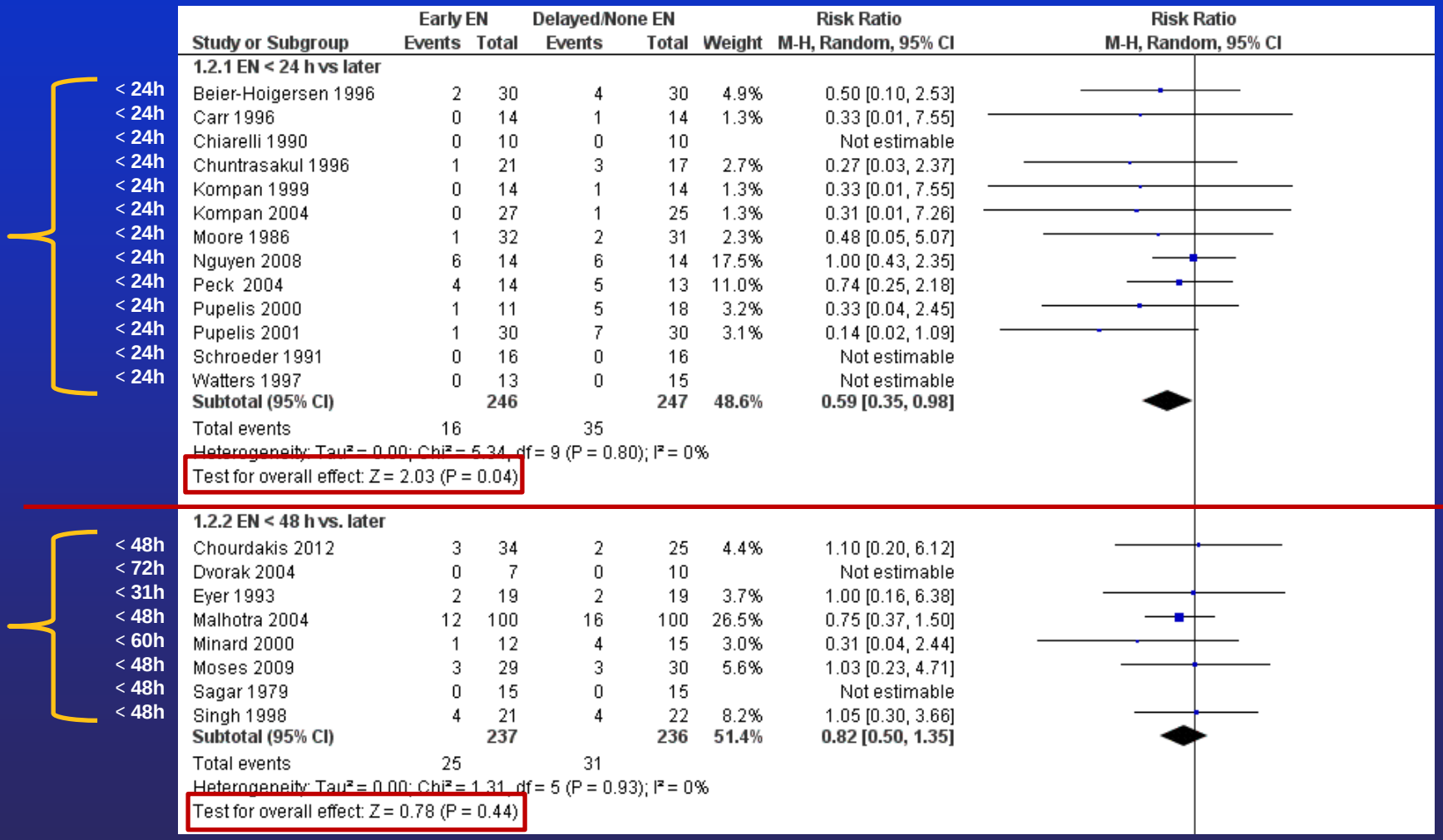
2016 SCCM and ASPEN guideline (eEN < 48h)



	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
	Heterogeneity: Tau² = 0.00; Chi² = 5.34, df = 9 (P = 0.80); I² = 0%						
	Test for overall effect: Z = 2.03 (P = 0.04)						
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Subtotal (95% CI)		**237**		**236**	**51.4%**	**0.82 [0.50, 1.35]**
	Total events	25		31			
	Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 5 (P = 0.93); I² = 0%						
	Test for overall effect: Z = 0.78 (P = 0.44)						

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)



	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	10		Not estimable
< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
< 24h	Kompan 1999	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]
< 24h	Moore 1986	1	32	2	31	2.3%	0.48 [0.05, 5.07]
< 24h	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]
< 24h	Peck 2004	4	14	5	13	11.0%	0.74 [0.25, 2.18]
< 24h	Pupelis 2000	1	11	5	18	3.2%	0.33 [0.04, 2.45]
< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]
< 24h	Schroeder 1991	0	16	0	16		Not estimable
< 24h	Watters 1997	0	13	0	15		Not estimable
	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
	Heterogeneity: Tau² = 0.00; Chi² = 5.34, df = 9 (P = 0.80); I² = 0%						
	Test for overall effect: Z = 2.03 (P = 0.04)						
	1.2.2 EN < 48 h vs. later						
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]
< 72h	Dvorak 2004	0	7	0	10		Not estimable
< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
< 48h	Sagar 1979	0	15	0	15		Not estimable
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Subtotal (95% CI)		**237**		**236**	**51.4%**	**0.82 [0.50, 1.35]**
	Total events	25		31			
	Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 5 (P = 0.93); I² = 0%						
	Test for overall effect: Z = 0.78 (P = 0.44)						

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

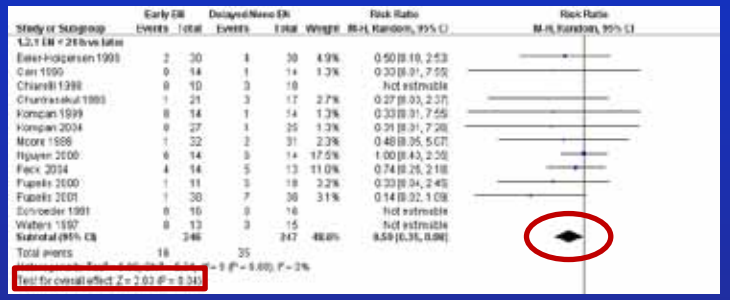
- Most recent SCCM/ASPEN guideline includes 21 clinical trials

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

- Most recent SCCM/ASPEN guideline includes 21 clinical trials

- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).



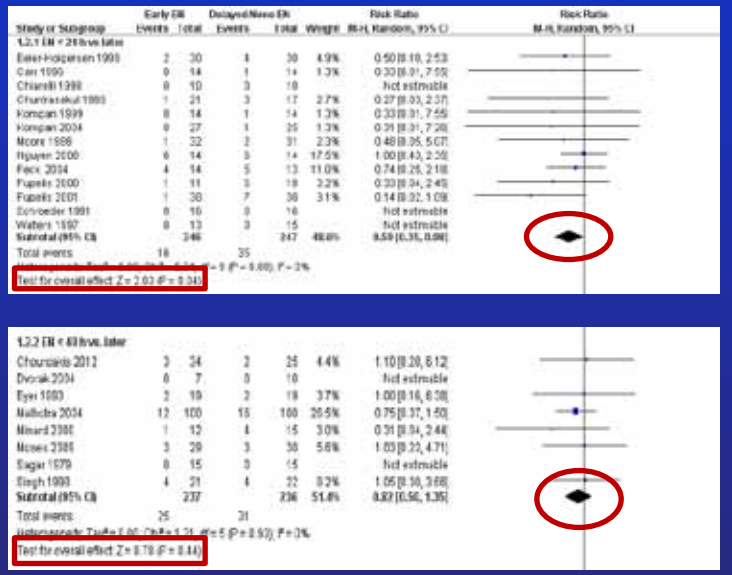
McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

- Most recent SCCM/ASPEN guideline includes 21 clinical trials

- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).

- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44) .



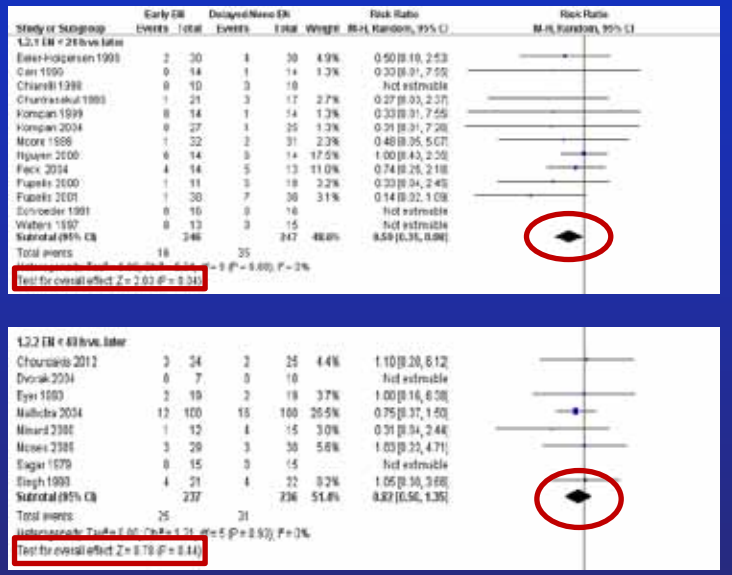
McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

- Most recent SCCM/ASPEN guideline includes 21 clinical trials

- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).

- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44) .



There is no evidence of mortality benefit if we wait longer than 24 h!!

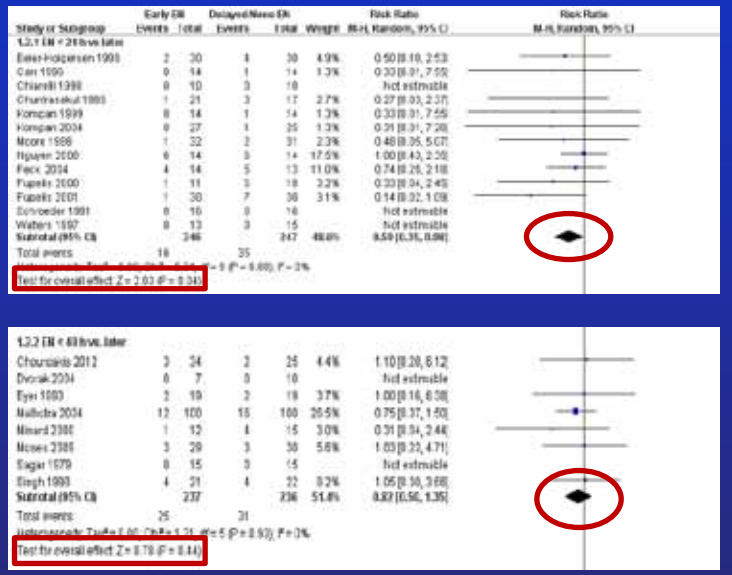
McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

2016 SCCM and ASPEN guideline (eEN < 48h)

- Most recent SCCM/ASPEN guideline includes 21 clinical trials

- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).

- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44) .



There is no evidence of mortality benefit if we wait longer than 24 h!!

Why?

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Energy sources in health and critical illness

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.
- After glycogen is depleted, the body adapts to using fat stores as an energy source, *mediated by continued low insulin levels*.

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.
- After glycogen is depleted, the body adapts to using fat stores as an energy source, *mediated by continued low insulin levels*.

Critical illness, trauma and burn injury result in a *hypermetabolic state*.

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.
- After glycogen is depleted, the body adapts to using fat stores as an energy source, *mediated by continued low insulin levels*.

Critical illness, trauma and burn injury result in a *hypermetabolic state*.

- Characterised by hyperglycaemia, insulin insensitivity and high circulating insulin.

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.
- After glycogen is depleted, the body adapts to using fat stores as an energy source, *mediated by continued low insulin levels*.

Critical illness, trauma and burn injury result in a *hypermetabolic state*.

- Characterised by hyperglycaemia, insulin insensitivity and high circulating insulin.
- There is a block on using fat stores, *mediated by high insulin state (?)*

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

Energy sources in health and critical illness

In a healthy person, fasting results in down regulation of the metabolic rate to conserve all stored nutrients (*hypometabolic state*).

- Characterised by low blood glucose levels and low circulating insulin.
- After glycogen is depleted, the body adapts to using fat stores as an energy source, *mediated by continued low insulin levels*.

Critical illness, trauma and burn injury result in a *hypermetabolic state*.

- Characterised by hyperglycaemia, insulin insensitivity and high circulating insulin.
- There is a block on using fat stores, *mediated by high insulin state (?)*
- After glycogen is depleted, *protein* becomes the primary energy source.

Preiser J-C, Ichai C, Orban J-C and Groeneveld ABJ. Metabolic response to the stress of critical illness. *British Journal of Anaesthesia* **2014**; 113(6): 945–54

When are glycogen stores depleted?

When are glycogen stores depleted?

- Glycogen is a multibranched polysaccharide of glucose that serves as a form of immediately available energy

David H. Wasserman. Four grams of glucose. *Am J Physiol Endocrinol Metab* **2009** Jan; 296(1): E11–E21.

When are glycogen stores depleted?

- Glycogen is a multibranched polysaccharide of glucose that serves as a form of immediately available energy
- In humans, glycogen is stored primarily in the liver (90 to 160 gms) and skeletal muscles (400 - 600 gms)
  - *Each gram of glycogen results in 4 kcals of usable energy*.

David H. Wasserman. Four grams of glucose. *Am J Physiol Endocrinol Metab* **2009** Jan; 296(1): E11–E21.

When are glycogen stores depleted?

- Glycogen is a multibranched polysaccharide of glucose that serves as a form of immediately available energy
- In humans, glycogen is stored primarily in the liver (90 to 160 gms) and skeletal muscles (400 - 600 gms)
  - *Each gram of glycogen results in 4 kcals of usable energy*.
- But, muscle glycogen appears to function only as an immediate source of glucose for muscle action.
- So, the rest of our metabolic needs must be met by liver glycogen
  - 90 to 160 g liver glycogen results in 350 to 650 kcals

David H. Wasserman. Four grams of glucose. *Am J Physiol Endocrinol Metab* **2009** Jan; 296(1): E11–E21.

When are glycogen stores depleted?

- Glycogen is a multibranched polysaccharide of glucose that serves as a form of immediately available energy
- In humans, glycogen is stored primarily in the liver (90 to 160 gms) and skeletal muscles (400 - 600 gms)
  - *Each gram of glycogen results in 4 kcals of usable energy*.
- But, muscle glycogen appears to function only as an immediate source of glucose for muscle action.
- So, the rest of our metabolic needs must be met by liver glycogen
  - 90 to 160 g liver glycogen results in 350 to 650 kcals

Glycogen stores last less than a day!

David H. Wasserman. Four grams of glucose. *Am J Physiol Endocrinol Metab* **2009** Jan; 296(1): E11–E21.

Proteolysis starts early in critical illness

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.
- Which sources of protein are catabolised during critical illness?

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.
- Which sources of protein are catabolised during critical illness?
  - *muscle*

Sequential Changes in the Metabolic Response in Critically Injured Patients During the First 25 Days After Blunt Trauma

David N. Monk, M.B., Ch.B.,* Lindsay D. Plank, D.Phil.,* Guzmán Franch-Arcas, M.D.,* Patrick J. Finn, M.B., Ch.B.,* Stephen J. Streat, M.B., Ch.B.,† and Graham L. Hill, M.D.*

From the University Department of Surgery and Department of Critical Care Medicine,† Auckland Hospital, Auckland, New Zealand*

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.
- Which sources of protein are catabolised during critical illness?
  - *muscle*
  - *diaphragm*

Sequential Changes in the Metabolic Response in Critically Injured Patients During the First 25 Days After Blunt Trauma

David N. Monk, M.B., Ch.B.,* Lindsay D. Plank, D.Phil.,* Guzmán Franch-Arcas, M.D.,* Patrick J. Finn, M.B., Ch.B.,* Stephen J. Streat, M.B., Ch.B.,† and Graham L. Hill, M.D.*

From the University Department of Surgery and Department of Critical Care Medicine,† Auckland Hospital, Auckland, New Zealand*

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.
- Which sources of protein are catabolised during critical illness?
  - *muscle*
  - *diaphragm*
  - *gastrointestinal barrier cells*

Sequential Changes in the Metabolic Response in Critically Injured Patients During the First 25 Days After Blunt Trauma

David N. Monk, M.B., Ch.B.,* Lindsay D. Plank, D.Phil.,* Guzmán Franch-Arcas, M.D.,* Patrick J. Finn, M.B., Ch.B.,* Stephen J. Streat, M.B., Ch.B.,† and Graham L. Hill, M.D.*

From the University Department of Surgery and Department of Critical Care Medicine,† Auckland Hospital, Auckland, New Zealand*

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Proteolysis starts early in critical illness

- Glycogen stores last less than a day.
- In critical illness, up-regulation of proteolysis begins as soon as liver glycogen is depleted, to provide amino acids to fuel gluconeogenesis.
- Which sources of protein are catabolised during critical illness?
  - *muscle*
  - *diaphragm*
  - *gastrointestinal barrier cells*
  - *brain*

Sequential Changes in the Metabolic Response in Critically Injured Patients During the First 25 Days After Blunt Trauma

David N. Monk, M.B., Ch.B.,* Lindsay D. Plank, D.Phil.,* Guzmán Franch-Arcas, M.D.,* Patrick J. Finn, M.B., Ch.B.,* Stephen J. Streat, M.B., Ch.B.,† and Graham L. Hill, M.D.*

From the University Department of Surgery and Department of Critical Care Medicine,† Auckland Hospital, Auckland, New Zealand*

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. *Neurocrit Care* **2017**;26:348-355.

Diaphragmatic function

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

What do we know about autophagy?

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Autophagy

Autophagy

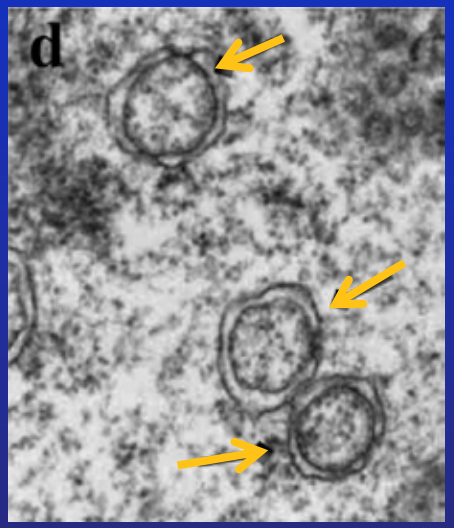
A process that ‘denatures and digests’ cellular structures using characteristic double-membrane vesicles called autolysosomes.

Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

Autophagy

Autophagy

A process that ‘denatures and digests’ cellular structures using characteristic double-membrane vesicles called autolysosomes.



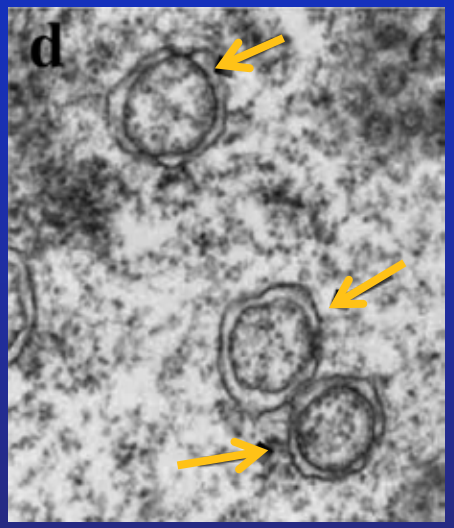
Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

Autophagy

Autophagy

A process that 'denatures and digests' cellular structures using characteristic double-membrane vesicles called autolysosomes.

Autophagy eliminates damaged proteins and organelles tagged with *ubiquitin*.



Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

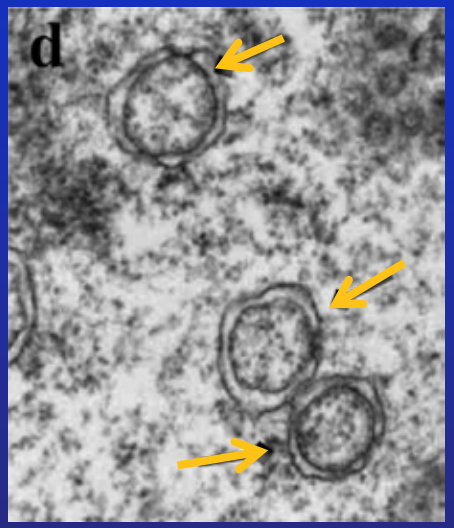
Autophagy

Autophagy

A process that 'denatures and digests' cellular structures using characteristic double-membrane vesicles called autolysosomes.

Autophagy eliminates damaged proteins and organelles tagged with *ubiquitin*.

Approximately 50 years ago, it was first recognised that autophagy was massively increased during nutrient starvation.



Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

Autophagy

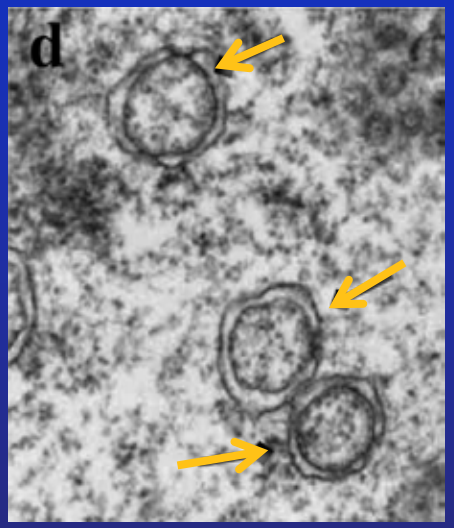
Autophagy

A process that 'denatures and digests' cellular structures using characteristic double-membrane vesicles called autolysosomes.

Autophagy eliminates damaged proteins and organelles tagged with *ubiquitin*.

Approximately 50 years ago, it was first recognised that autophagy was massively increased during nutrient starvation.

During starvation, autolysosomes do not just target damaged structures. Their action is 'non-selective'.



Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

Autophagy

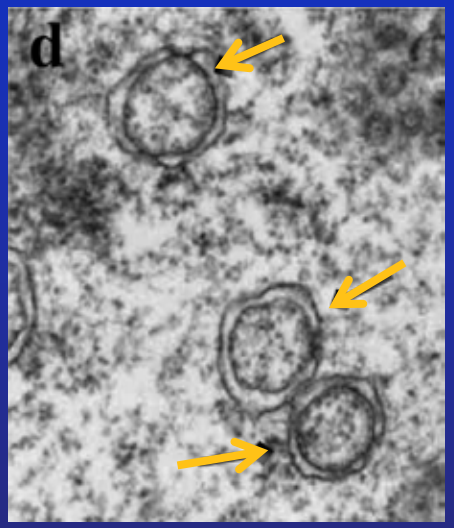
Autophagy

A process that 'denatures and digests' cellular structures using characteristic double-membrane vesicles called autolysosomes.

Autophagy eliminates damaged proteins and organelles tagged with *ubiquitin*.

Approximately 50 years ago, it was first recognised that autophagy was massively increased during nutrient starvation.

During starvation, autolysosomes do not just target damaged structures. Their action is 'non-selective'.



"In nutrient deprivation, autophagy activates bulk protein (non-selective) degradation to harvest amino acids as a fuel for ATP production through the tricarboxylic acid (TCA) cycle."

Kook Hwan Kim & Myung-Shik Lee. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* **2014**;15(1):11-20

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

"we speculate that blocking or attenuating diaphragm proteolytic pathways in patients on mechanical ventilation might mitigate the weaning problems that occur in some patients."

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Diaphragmatic function

Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only 18 h of mechanical ventilation
- Significant increase in diaphragmatic proteolysis, characterised as autophagy by electron micrograph, after as little as 15 h of mechanical ventilation

"we speculate that blocking or attenuating diaphragm proteolytic pathways in patients on mechanical ventilation might mitigate the weaning problems that occur in some patients."

Protein intake down regulates autophagy by a factor of 2 to 5 times within 20 minutes.

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **2008** Mar 27;358(13):1327-35.

Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med* **2010** Dec 1;182(11):1377-86.

Focusing on autophagy. *Nature Cell Biology* **2010**;12:813.

Gut barrier function

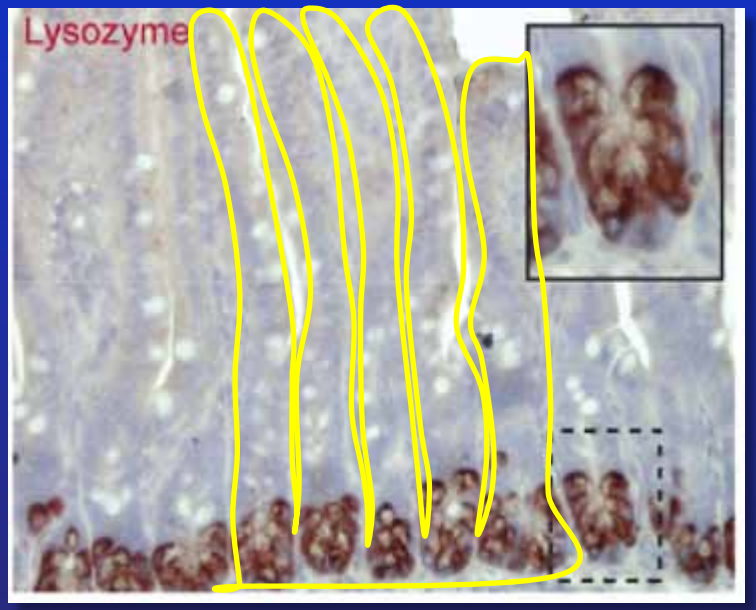
Gut barrier function

- *Paneth cells* are highly specialized epithelial cells located in the crypts of the small intestine.

Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV: Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. *Proc Natl Acad Sci USA* **2008**, 105:20858–20863

Gut barrier function

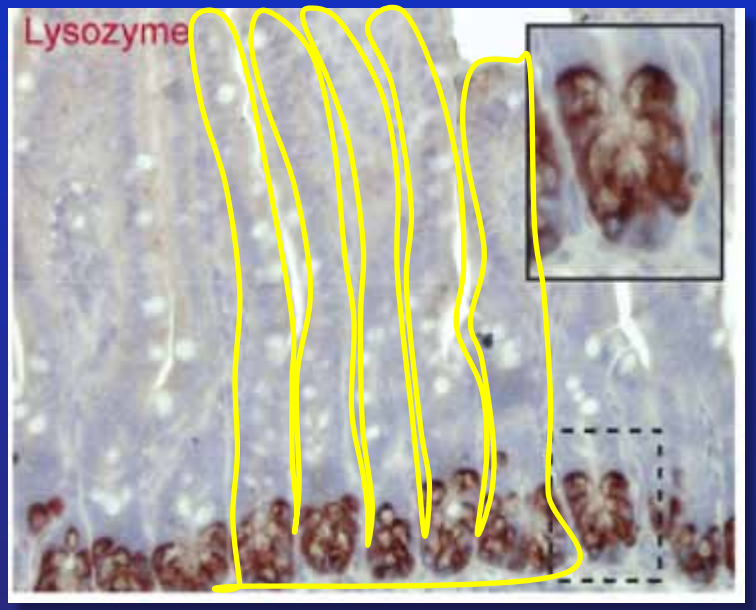
- *Paneth cells* are highly specialized epithelial cells located in the crypts of the small intestine.



Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV: Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. *Proc Natl Acad Sci USA* **2008**, 105:20858–20863

Gut barrier function

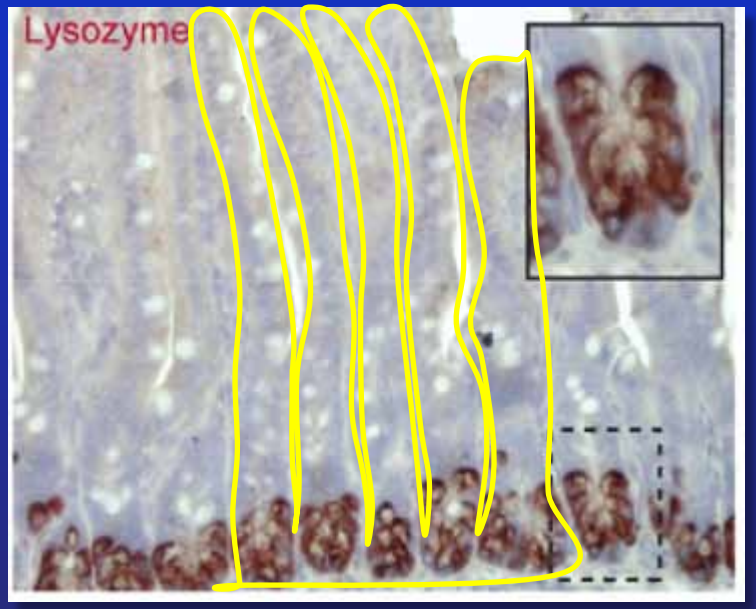
- *Paneth cells* are highly specialized epithelial cells located in the crypts of the small intestine.
- They are the main producers of antimicrobial proteins in the gut.
- Create and secrete granules containing antimicrobial peptides.
  - Lysozyme , α-defensins plus



Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV: Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. *Proc Natl Acad Sci USA* **2008**, 105:20858–20863

Gut barrier function

- *Paneth cells* are highly specialized epithelial cells located in the crypts of the small intestine.
- They are the main producers of antimicrobial proteins in the gut.
- Create and secrete granules containing antimicrobial peptides.
  - Lysozyme , α-defensins plus
- These antimicrobial peptides protect against bacterial translocation and also protect the gut stem cells from damage.



Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV: Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. *Proc Natl Acad Sci USA* **2008**, 105:20858–20863

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.
- 48 h of fasting led to:

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.
- 48 h of fasting led to:
  - a significant reduction in antimicrobial peptide production ($P<0.01$ by quantitative western blot assay and quantitative PCR).

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.
- 48 h of fasting led to:
  - a significant reduction in antimicrobial peptide production ($P<0.01$ by quantitative western blot assay and quantitative PCR).
  - 2-fold increase in bacterial translocation ($P<0.01$ for increase in CFUs cultured from mesenteric lymph node tissue).

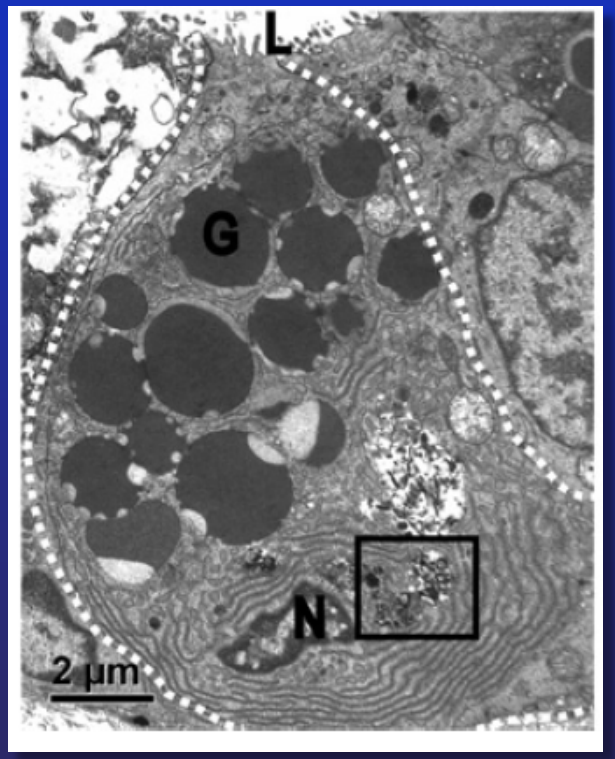
Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Gut barrier function

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.
- 48 h of fasting led to:
  - a significant reduction in antimicrobial peptide production ($P<0.01$ by quantitative western blot assay and quantitative PCR).
  - 2-fold increase in bacterial translocation ($P<0.01$ for increase in CFUs cultured from mesenteric lymph node tissue).
  - *structural changes that explained these functional correlates.*

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

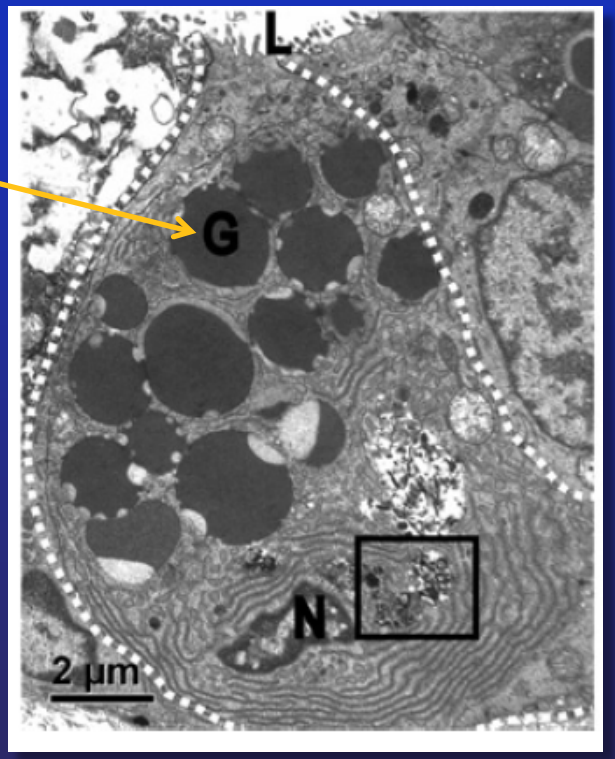
Gut barrier function



Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* 2011;179:2885-2893.

Gut barrier function

Antimicrobial protein globules

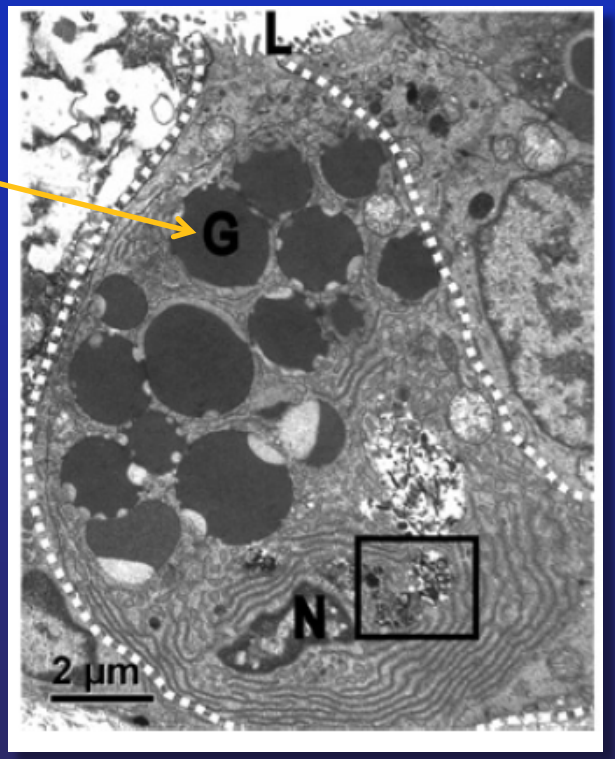


Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* 2011;179:2885-2893.

Gut barrier function

Globules to be secreted into lumen of small intestine

Antimicrobial protein globules

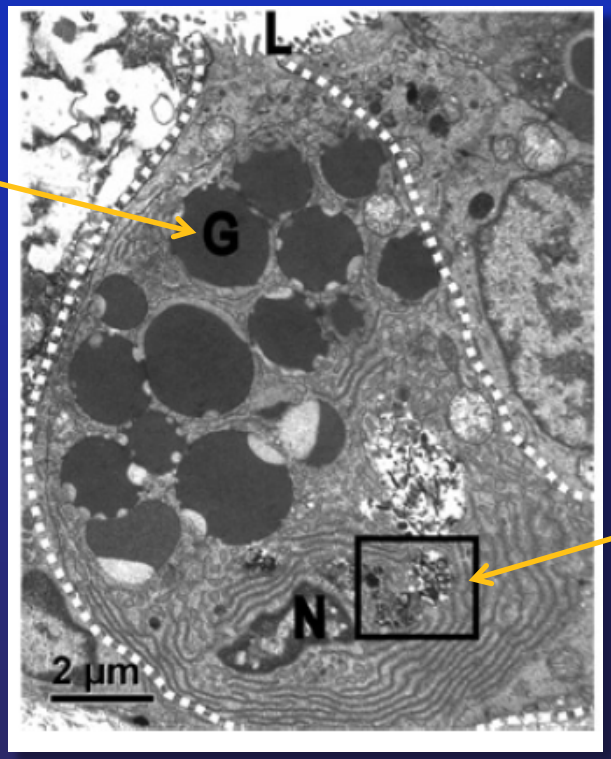


Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* 2011;179:2885-2893.

Gut barrier function

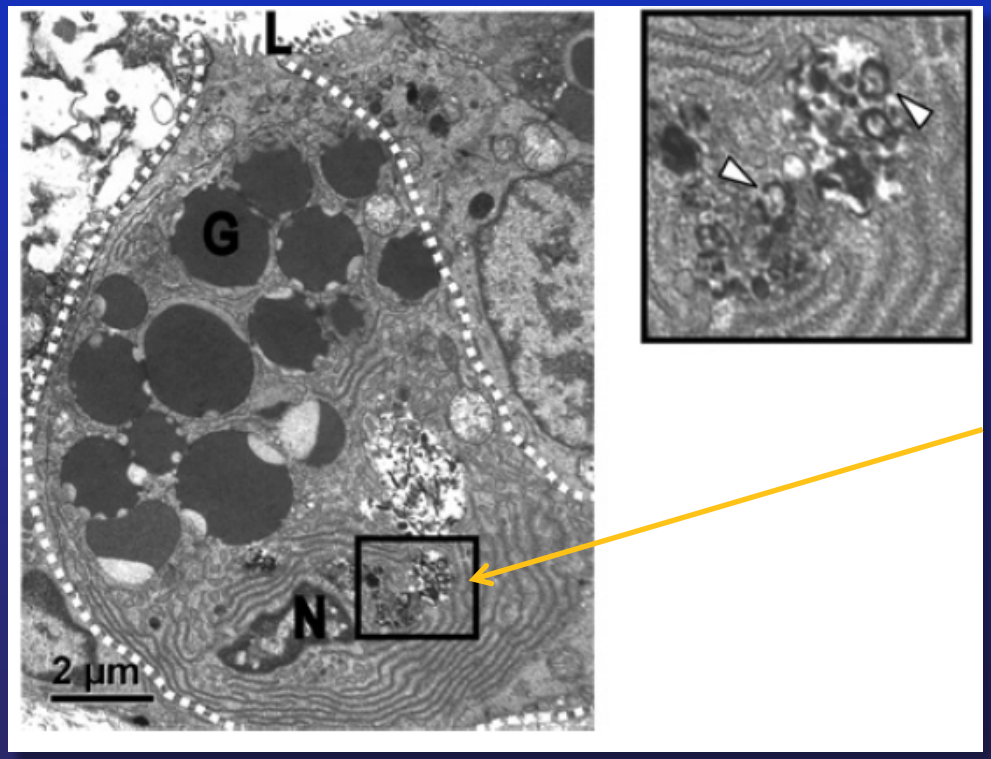
Globules to be secreted into lumen of small intestine

Antimicrobial protein globules



Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* 2011;179:2885-2893.

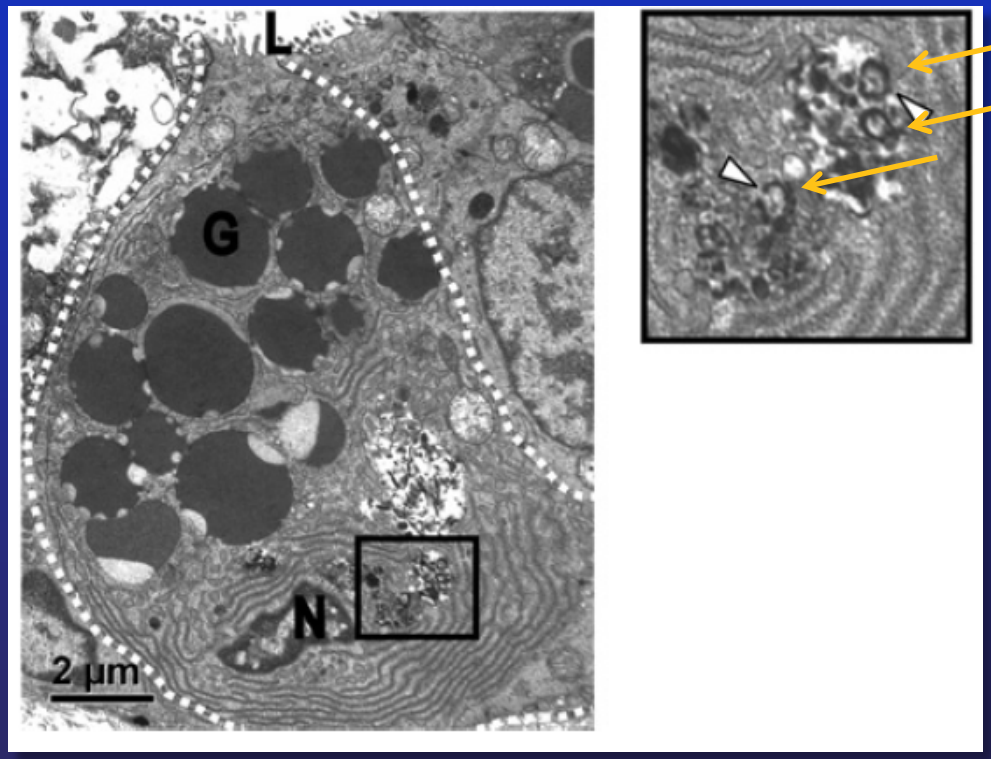
Gut barrier function



Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* 2011;179:2885-2893.

Gut barrier function

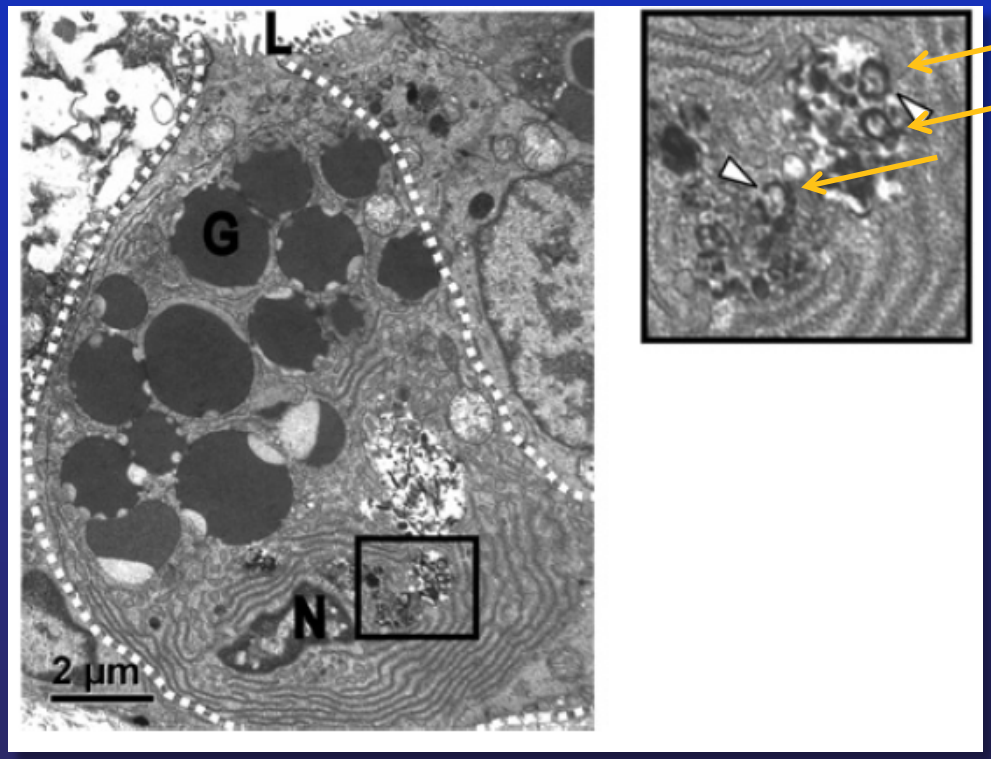
- Fasting led to proteolysis in Paneth cells, with significant increase in *late-stage degradative autophagolysosomes (autophagy)*.



Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. ***Am J Path*** 2011;179:2885-2893.

Gut barrier function

- Fasting led to proteolysis in Paneth cells, with significant increase in *late-stage degradative autophagolysosomes (autophagy)*.
- Increase in autophagy compromised Paneth cell gut-barrier function



Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. ***Am J Path*** 2011;179:2885-2893.

Traumatic brain injury (TBI)

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

- Assays for p62 and Beclin 1 increased significantly over time, indicating ongoing proteolysis (autophagy).

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

- Assays for p62 and Beclin 1 increased significantly over time, indicating ongoing proteolysis (autophagy).
- After controlling for age and initial GCS, higher peak levels were independently associated with worse functional outcomes.

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

- Assays for p62 and Beclin 1 increased significantly over time, indicating ongoing proteolysis (autophagy).
- After controlling for age and initial GCS, higher peak levels were independently associated with worse functional outcomes.

Tissue samples were obtained from adults who underwent a decompressive craniectomy as management for high intracranial pressure after TBI

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Clark RSB, Bayir H, Chu CT,Alber SM, Kochanek PM and Watkins SC. Autophagy is increased in mice after brain injury and is dectetectable in human brain after trauma and critical illness. ***Authophagy*** 2008;4:1,88-90.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

- Assays for p62 and Beclin 1 increased significantly over time, indicating ongoing proteolysis (autophagy).
- After controlling for age and initial GCS, higher peak levels were independently associated with worse functional outcomes.

Tissue samples were obtained from adults who underwent a decompressive craniectomy as management for high intracranial pressure after TBI

- Assays for protein LC3-II and Beclin 1 found evidence of ongoing proteolysis (autophagy) that peaked at 24 h post-injury.

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Clark RSB, Bayir H, Chu CT,Alber SM, Kochanek PM and Watkins SC. Autophagy is increased in mice after brain injury and is dectetectable in human brain after trauma and critical illness. ***Authophagy*** 2008;4:1,88-90.

Traumatic brain injury (TBI)

Autophagy can be detected using biochemical markers.

CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

- Assays for p62 and Beclin 1 increased significantly over time, indicating ongoing proteolysis (autophagy).
- After controlling for age and initial GCS, higher peak levels were independently associated with worse functional outcomes.

Tissue samples were obtained from adults who underwent a decompressive craniectomy as management for high intracranial pressure after TBI

- Assays for protein LC3-II and Beclin 1 found evidence of ongoing proteolysis (autophagy) that peaked at 24 h post-injury.
- None of these patients had started feeding prior to the time of the biopsy.

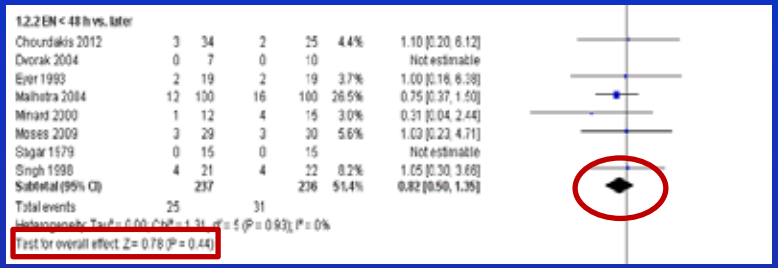
Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. ***Neurocrit Care*** 2017;26:348-355.

Clark RSB, Bayir H, Chu CT,Alber SM, Kochanek PM and Watkins SC. Autophagy is increased in mice after brain injury and is dectetectable in human brain after trauma and critical illness. ***Authophagy*** 2008;4:1,88-90.

Starting feeding later than 24 h

Starting feeding later than 24 h

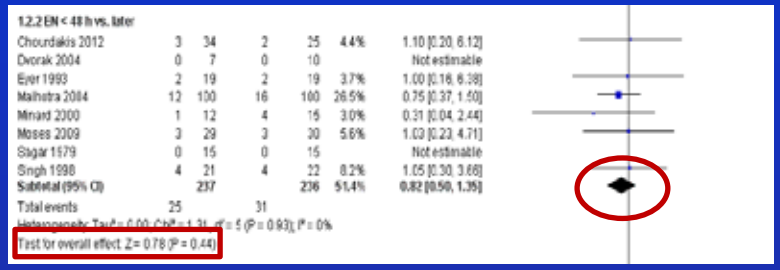
- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding later than 24 h

- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).

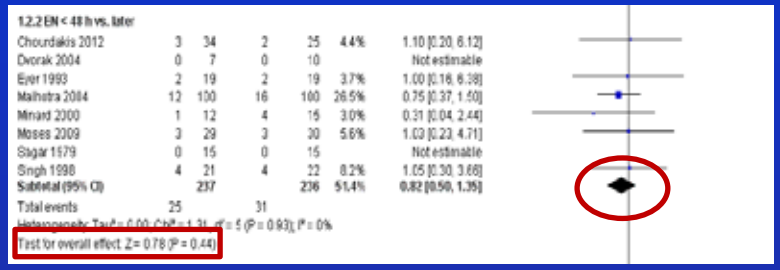


- Furthermore, delay for longer than 24 h depletes liver glycogen stores and stimulates proteolysis:

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding later than 24 h

- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).



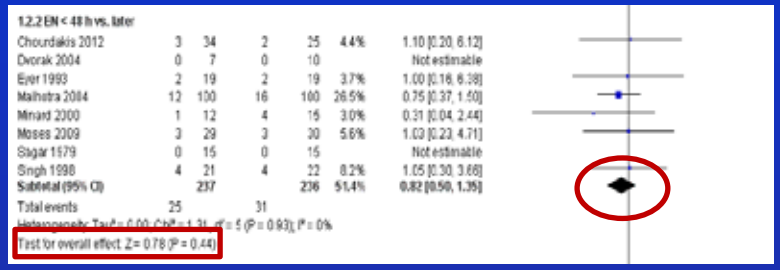
- Furthermore, delay for longer than 24 h depletes liver glycogen stores and stimulates proteolysis:
  - impacts diaphragmatic function,

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. **2008** Mar 27;358(13):1327-35.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding later than 24 h

- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).



- Furthermore, delay for longer than 24 h depletes liver glycogen stores and stimulates proteolysis:
  - impacts diaphragmatic function,
  - gut barrier function,

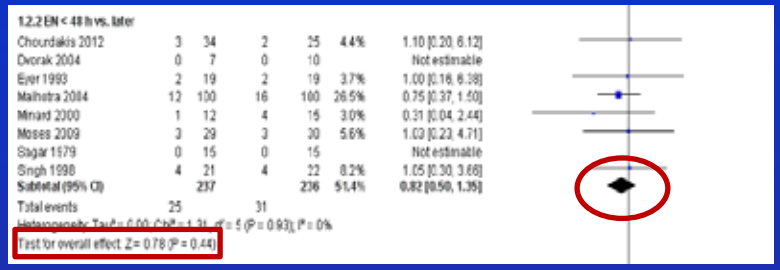
Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. **2008** Mar 27;358(13):1327-35.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding later than 24 h

- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).



- Furthermore, delay for longer than 24 h depletes liver glycogen stores and stimulates proteolysis:
  - impacts diaphragmatic function,
  - gut barrier function,
  - and perhaps even brain function (delirium, long-term cognitive impairment).

Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Authophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. *Neurocrit Care* **2017**;26:348-355.

Hodin CM, Lenaerts K, Grootjans J, de Haan JJ, Hadfoune M, Verheyen FK, Kiyama H, Keineman E and Buurman WA. Starvation compromises Paneth Cells. *Am J Path* **2011**;179:2885-2893.

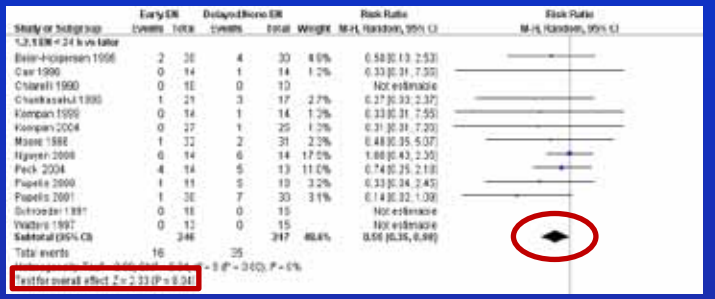
Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. **2008** Mar 27;358(13):1327-35.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding within 24 h

Starting feeding within 24 h

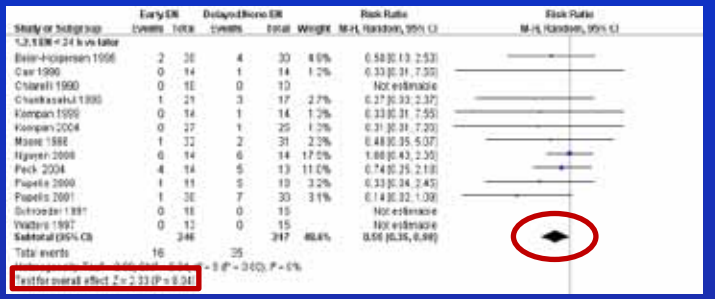
- 2016 SCCM/ASPEN guideline
- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: : SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding within 24 h

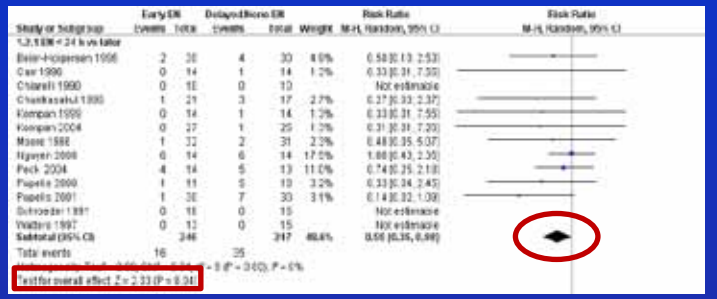
- 2016 SCCM/ASPEN guideline
- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).
- Furthermore, early (<24 h) nutrition:



McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: : SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding within 24 h

- 2016 SCCM/ASPEN guideline
- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).



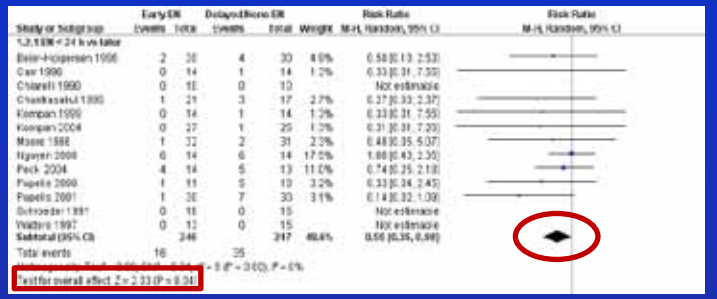
- Furthermore, early (<24 h) nutrition:
  - May preserve diaphragmatic function (duration of mechanical ventilation reduced by 2.34 days, P=0.06).

Doig GS, Checrou-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.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: : SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding within 24 h

- 2016 SCCM/ASPEN guideline
- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).



- Furthermore, early (<24 h) nutrition:
  - May preserve diaphragmatic function (duration of mechanical ventilation reduced by 2.34 days, P=0.06).
  - Preserves gut barrier function (reduced GI haemorrhage P=0.0005; sepsis P<0.0001; and pneumonia P=0.01).

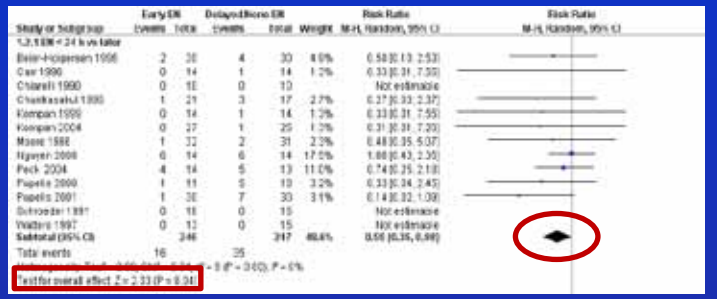
PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Checrou-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.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: : SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Starting feeding within 24 h

- 2016 SCCM/ASPEN guideline
- Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).



- Furthermore, early (<24 h) nutrition:
  - May preserve diaphragmatic function (duration of mechanical ventilation reduced by 2.34 days, P=0.06).
  - Preserves gut barrier function (reduced GI haemorrhage P=0.0005; sepsis P<0.0001; and pneumonia P=0.01).
  - *In a mouse model of TBI, partially inhibited autophagy leading to improvements in behavioural and histological outcomes.*

Lai Y, Hickey RW, Chen Y, Bayir H, et al. Autophagy is increased after TBI in mice and is partially inhibited by the antioxident gamma-glutamlcysteinly ethyl ester. *J Cereb Blood Flow Metab* **2008**;28(3):540-550.

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Checrou-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.

McClave SA, Taylor BE, Martindale RG, *et al*. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: : SCCM and ASPEN. *J Parenter Enteral Nutr* **2016**;40(2):159-211.

Summary

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h	*Daren Heyland’s Canadian guideline,*	Trend towards mortality reduction.
< 48 h	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 48 h	*American (SCCM and ASPEN) guideline*	Significant mortality reduction

Summary

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h	*Daren Heyland’s Canadian guideline,*	Trend towards mortality reduction.
< 48 h	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 48 h	*American (SCCM and ASPEN) guideline*	Significant mortality reduction

Summary

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h –	*Daren Heyland’s Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
~~< 48~~ h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction

There is no evidence of mortality benefit if EN is started *later than 24 h.*

Summary

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

< 48 h –	*Daren Heyland’s Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 24 h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction.

There is no evidence of mortality benefit if EN is started *later than 24 h.*

Based on clinical trials in updated meta-analyses, we recommend that EN should begin within 24 h of ICU admission

Summary

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

< 48 h –	*Daren Heyland's Canadian guideline,*	Trend towards mortality reduction.
< 48 h –	*European (ESPEN) guideline,*	No effect on mortality.
< 24 h –	*ACCEPT guideline (also Canadian),*	Significant mortality reduction.
< 24 h –	*Australian and New Zealand guideline,*	Significant mortality reduction.
< 24 h –	*American (SCCM and ASPEN) guideline*	Significant mortality reduction.

There is no evidence of mortality benefit if EN is started *later than 24 h.*

Based on clinical trials in updated meta-analyses, we recommend that EN should begin within 24 h of ICU admission, as soon as shock is stabilised:

- 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.

Assorted loose ends

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

- EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
  - 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.

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

- EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
  - 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.
- Rates and Targets
  - There is no robust evidence to mandate specific rates or goals.
  - In general, start slow and achieve reasonable goals within 3 to 7 days.

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Assorted loose ends

- EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
  - 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.
- Rates and Targets
  - There is no robust evidence to mandate specific rates or goals.
  - In general, start slow and achieve reasonable goals within 3 to 7 days.
- Gut Dysmotility
  - Mounting evidence suggests *we* create gut dysmotility by feeding late.
  - Gastric tubes are easier to place and allow you to start earlier.
  - Do not allow the placement of a post-pyloric tube to delay EN.

PU H, Doig GS, Heighes PT and Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: A meta-analysis of RCTs. *Crit Care Med* **2018**;46(12):2036-2042.

Doig GS, Heighes PT, Simpson F and Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56

Tian F, Heighes PT, Allingstrup MJ and Doig GS. Early enteral nutrition provided within 24 h of ICU admission: A meta-analysis of randomized controlled trials. Crit Care Med. 2018 46(7):1049-1056.[Editor's Choice]

Questions?

A pdf version of this talk can be downloaded from the Talks section of our outreach education web site (www.EvidenceBased.net).