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

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- Discuss physiological ramifications.
- Present clinical evidence that supports the physiology.
- Conclude.



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	Early E		Delayed/No			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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]	<b>+</b>
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: Tau <sup>2</sup> = 0.1	00; Chi <b>²</b> = 1	7.23, d	lf = 15 (P = 0	.95); I² =	0%		
Test for overall effect: Z =	- = 1.97 (P =	0.05)					0.01 0.1 1 1 10 100 Favours [experimental] Favours [control]
Test for subaroup differe	ences: Chi	² = 0.8·	4. df = 1 (P =	0.36), I <sup>2</sup> :	= 0%		ravours (experimental) ravours (control)



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

Recommends early EN within 24 to 48 h of ICU admission



	Study or Subgroup	Early E Events		Delayed/Non Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
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	Study or Subgroup	Early E Events		Delayed/Non Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
< 24h < 31h < 48h < 31h < 48h < 60h	Beier-Hoigersen 1996 Carr 1996 Chiarelli 1990 Chuntrasakul 1996 Kompan 1999 Kompan 2004 Moore 1986 Nguyen 2008 Peck 2004 Pupelis 2000 Pupelis 2001 Schroeder 1991 Watters 1997 Chourdakis 2012 Dvorak 2004 Eyer 1993 Malhotra 2004 Minard 2000	2 0 1 0 1 6 4 1 1 0 3 0 2 12 1	30 14 10 21 14 27 32 14 14 11 30 16 13 34 7 19 100 12	4 1 3 1 2 6 5 5 7 0 2 0 2 0 2 16 4	30 14 10 17 14 25 31 14 13 18 30 16 15 25 10 19 100 15	4.9% 1.3% 2.7% 1.3% 2.3% 17.5% 11.0% 3.2% 3.1% 4.4% 3.7% 26.5% 3.0%	0.50 [0.10, 2.53] 0.33 [0.01, 7.55] Not estimable 0.27 [0.03, 2.37] 0.33 [0.01, 7.55] 0.31 [0.01, 7.26] 0.48 [0.05, 5.07] 1.00 [0.43, 2.35] 0.74 [0.25, 2.18] 0.33 [0.04, 2.45] 0.14 [0.02, 1.09] Not estimable 1.10 [0.20, 6.12] Not estimable 1.00 [0.16, 6.38] 0.75 [0.37, 1.50] 0.31 [0.04, 2.44]	
< 48h < 48h < 48h	Moses 2009 Sagar 1979 Singh 1998	3 0 4	29 15 21	3 0 4	30 15 22	5.6% 8.2%	1.03 (0.23, 4.71) Not estimable 1.05 (0.30, 3.66)	
	Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = Test for subgroup differe	1.97 (P =	0.05)	,	5); I² = I		0.70 [0.49, 1.00]	O.01 0.1 1 10 100 Favours [experimental] Favours [control]

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

Recommends early EN within 24 to 48 h of ICU admission



	Study of Subgroup	Early E Events		Delayed/Nor Events		Maight	Risk Ratio	Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
0.41	D : U :		~~		~~			
< 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: Tau <sup>2</sup> – 0.		<u>4 25 7</u>		95): I <sup>2</sup> = I	0%		
	Test for overall effect: Z =	•		.=	00/11 = 1	0.00		0.01 0.1 1 10 100
	lest for subaroup differe			1 df = 1 (P = )	0 36) P	= 0%		Favours [experimental] Favours [control]

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

Recommends early EN within 24 to 48 h of ICU admission



		Early	EN	Delayed/No	ne EN		Risk Ratio	Risk Ratio
	Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	1.2.1 EN < 24 h vs later							
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]	<b>_</b>
< 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]	_ <b>+</b> _
< 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							I
< 48h	Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]	<b>-</b>
< 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]	<b>_</b>



		Early	EN	Delayed/No	ne EN		Risk Ratio	Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	1.2.1 EN < 24 h vs later							
< 24ł		2	30	4	30	4.9%	0.50 [0.10, 2.53]	
< <b>24</b> ł		0	14	1	14	1.3%	0.33 [0.01, 7.55]	
< 24ł	Chiarelli 1990	0	10	0	10		Not estimable	
< 24ľ		1	21	3	17	2.7%	0.27 [0.03, 2.37]	
< 24ł	rienipan reee	0	14	1	14	1.3%	0.33 [0.01, 7.55]	
< 24ł	riompan 2001	0	27	1	25	1.3%	0.31 [0.01, 7.26]	
< 24ł	1110010 1000	1	32	2	31	2.3%	0.48 [0.05, 5.07]	
< <b>24</b> ł		6	14	6	14	17.5%	1.00 [0.43, 2.35]	<b>+</b>
< 24ł		4	14	5	13	11.0%	0.74 [0.25, 2.18]	
< 24ł		1	11	5	18	3.2%	0.33 [0.04, 2.45]	
< 24ł		1	30	7	30	3.1%	0.14 [0.02, 1.09]	
< 24ł		0	16	0	16		Not estimable	
< 24ľ	Watters 1997	0	13	0	15		Not estimable	
	1.2.2 EN < 48 h vs. later							I
< 48ł		3	34	2	25	4.4%	1.10 [0.20, 6.12]	
< 72h	Dvorak 2004	0	7	0	10		Not estimable	
< 31h		2	19	2	19	3.7%	1.00 [0.16, 6.38]	
< 48ł	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]	
< 60ł	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]	
< 48ł	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]	
< 48ł	Sagar 1979	0	15	0	15		Not estimable	
< 48ł	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	
	-							



	Charles - Calanse	Early		Delayed/Nor		104-1-1-4	Risk Ratio	Risk Ratio
-	Study or Subgroup	Events	Total	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
< 24h	1.2.1 EN < 24 h vs later							
	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]	<b>_</b> _
< 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	<b>48.6</b> %	0.59 [0.35, 0.98]	◆
	Total events	16		35				
	Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>z</sup> =	5.34, d	f = 9 (P = 0.8	0); I <sup>z</sup> = 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]	<b></b>
	-							



	Study or Subgroup	Early Events		Delayed/No Events	ne EN Total	Woight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
	1.2.1 EN < 24 h vs later	Evenis	TUtai	Evenis	TULAI	weight	M-H, Kaluolli, 95% Cl	M-H, Rahuolii, 95% Ci
< 24		2	30	4	30	4.9%	0.50 [0.10, 2.53]	
< 24	Delet the geneen to be	2	- 30 14	4	30 14	4.9%	0.33 [0.01, 7.55]	
< 24	0411 1000	0	10	0	14	1.370	Not estimable	
< 24		1	21	3	10	2.7%	0.27 [0.03, 2.37]	
< 24	offatta acaitar reee	0	14	1	14	1.3%	0.33 [0.01, 7.55]	
< 24	riempan rece	0	27	1	25	1.3%	0.31 [0.01, 7.26]	
< 24	Rompan 2004	1	32	2	31	2.3%	0.48 [0.05, 5.07]	
< 24		6	14	6	14	17.5%	1.00 [0.43, 2.35]	
< 24		4	14	5	13	11.0%	0.74 [0.25, 2.18]	<b>_</b>
< 24		1	11	5	18	3.2%	0.33 [0.04, 2.45]	<b></b>
< 24		1	30	7	30	3.1%	0.14 [0.02, 1.09]	
< 24		O	16	O	16		Not estimable	
< 24		Ō	13	Ō	15		Not estimable	
	Subtotal (95% CI)	_	246	_	247	48.6%	0.59 [0.35, 0.98]	◆
	Total events	16		35				
	Heterogeneity: Tau <sup>2</sup> – 0.	00; Chi² –	5 34 d	f= 9 (P = 0.8	0); I <sup>z</sup> = 0	%		
	Test for overall effect: Z =	= 2.03 (P =	: 0.04)					
	1.2.2 EN < 48 h vs. later							
< 48		3	34	2	25	4.4%	1.10 [0.20, 6.12]	
< 72	Dividit 2004	0	7	0	10		Not estimable	
< 31	_,	2	19	2	19	3.7%	1.00 [0.16, 6.38]	
< 48	maniona 2001	12	100	16	100	26.5%	0.75 [0.37, 1.50]	
< 60	Initial a 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]	
< 48		3	29	3	30	5.6%	1.03 [0.23, 4.71]	
< 48		0	15	0	15		Not estimable	
	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]	
< 481	ollightiooo							
	olingii 1000							
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N									
			Early E		Delayed/No	ne EN		Risk Ratio	Risk Ratio
		Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
		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]	<b>_</b>
	< 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 <sup>2</sup> – 0.0			f= 9 (P = 0.8	0); I <sup>z</sup> = 0	%		
		Test for overall effect: Z =	: 2.03 (P =	: 0.04)					
	(0)	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]	



N			Early	EN	Delayed/Nor	IN EN		Risk Ratio	Risk Ratio
		Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	-	1.2.1 EN < 24 h vs later	LACIUS	Total	Lventa	Total	weight	m-n, random, 55% ci	M-H, Randoll, 55% Cl
	< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]	
	< 24h	Carr 1996	2	14	4	14	1.3%	0.33 [0.01, 7.55]	
	< 24h	Chiarelli 1990	0	10	, 0	10	1.570	Not estimable	
	< 24h	Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]	
	< 24h	Kompan 1999	N	14	1	14	1.3%	0.33 [0.01, 7.55]	
	< 24h	Kompan 2004	Ő	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 <sup>2</sup> – 0.(			f= 9 (P = 0.80	0); I <b>²</b> = 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: Tau <sup>2</sup> = 0.0	•		f = 5 (P = 0.93	3); I <sup>z</sup> = 0'	%		
		Test for overall effect: Z =	= 0.78 (P =	0.44)					



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		Study or Subgroup	Early		Delayed/Nor Events		Moight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio
		1.2.1 EN < 24 h vs later	Events	Total	Events	Total	weight	M-H, Kandom, 95% CI	M-H, Random, 95% Cl
$\sim$	< 24h			20		20	4.000	0 50 10 40 0 50	
	< 24h	Beier-Hoigersen 1996	2 0	30 14	4	30 14	4.9% 1.3%	0.50 [0.10, 2.53]	
	< 24h	Carr 1996 Chiarelli 1990	0	14 10	1 0	14	1.3%	0.33 [0.01, 7.55] Not estimable	
	< 24h	Chuntrasakul 1996	1	21	0 3	10	2.70		
	< 24h	Kompan 1999	י ח	14	3 1	14	2.7% 1.3%	0.27 [0.03, 2.37] 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	י ה	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]	<b>_</b>
	< 24h	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]	
	< 24h	Schroeder 1991	O	16	0	16	0.170	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 <sup>2</sup> – 0.	00; Chi <b>ž</b> –	5.34, d	f= 9 (P = 0.8	0); I <b>²</b> = 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 < 60h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]	
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			25	251	31	250	J 1.470	0.02 [0.50, 1.55]	
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- After glycogen is depleted, *protein* becomes the primary energy source.





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A process that 'denatures and digests' cellular structures using characteristic doublemembrane vesicles called autolysosomes.

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## 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

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

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- They are the main producers of antimicrobial proteins in the gut.
- Create and secrete granules containing antimicrobial peptides.
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- They are the main producers of antimicrobial proteins in the gut.
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- These antimicrobial peptides protect against bacterial translocation and also protect the gut stem cells from damage.





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  - structural changes that explained these functional correlates.







# Antimicrobial protein globules







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.

92





Antimicrobial protein globules







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- 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







Autophagy can be detected using biochemical markers.



Autophagy can be detected using biochemical markers. CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

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- None of these patients had started feeding prior to the time of the biopsy.

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

1.2.2 EN < 48 h vs. later									
Chourdakis 2012	3	34	2	25	4.4%	1.10 [0.20, 6.12]	<del></del>		
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)			
Subtotal (95% CI)		237		236	51.4%	0.82 [0.50, 1.35]	( 🔶 )		
Total events	25		31						
Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 1.31. df = 5 (P = 0.93); P = 0%									
Test for overall effect: $Z = 0.78$ (P = 0.44)									

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

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Study or subprove     Devents     Total     Weight     M.H., Random, 95% CI     M.H., Random, 95% CI       12.1 EH <21 hr vs. hter     12.1 EH <21 hr vs		Early	EN	Delayed/No	ne EN		Risk Ratio	Risk Ratio
Beler-Holgersen 1996     2     30     4     30     4.9%     0.50 [0.10, 2.53]       Carr 1996     0     1.4     1     1.4%     0.33 [0.01, 7.65]       Charlell 1990     0     0     0     0     Not estimable       Churtinsakul 1996     1     21     3     17     2.7%     0.37 [0.03, 2.37]       Kompan 1999     0     1.4     1     4.1     3.03 [0.01, 7.65]	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Carr 1986     0     14     1     14     1.3%     0.33 [0.01, 7.65]       Charell 1990     0     0     0     10     Not estimable       Churdmanskul 1986     1     21     3     17     27%     0.27 [0.03, 2.37]       Kompan 1998     0     14     1     41     12%     0.33 [0.01, 7.65]       Kompan 1998     0     14     1     41     0.33 [0.01, 7.65]	1.2.1 EN < 24 h vs later							
Chiareali 1990     0     10     0     10     Not estimable       Chundrussakul 1998     1     21     3     17     27%     0.27 [0.03, 2.37]       Kompan 1998     0     14     1     14     1.3%     0.33 [0.01, 55]       Kompan 1998     0     27     1     25     0.37 [0.03, 2.37]       Moore 1996     1     32     2     1.2%     0.40 [0.05, 507]       Nguyen 2008     6     1.4     6     1.4     1.5%     1.00 [0.43, 2.35]       Pupelic 2000     4     1.4     1.5%     0.31 [0.04, 2.45]     1.00 [0.43, 2.36]       Pupelic 2000     1     11     5     18     3.2%     0.33 [0.04, 2.45]       Pupelic 2000     1     10     7     30     3.1%     0.14 [0.02, 1.06]       Schroeder 1991     0     16     0     16     Not estimable       Viablotal (diSCtO)     2.46     2.47     48.6%     0.59 [0.35, 0.98]       Total events     16     35     0.50 [0.35, 0.98]     0.50 [0.35, 0.9	Beier-Holgersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]	
Churbarskul 1996     1     21     3     17     27%     0.27 [0.03, 2.37]       Kompan 1996     0     14     1     13%     0.33 [0.01, 7.65]       Kompan 2004     0     27     1     25     1.3%     0.33 [0.01, 7.65]       Moore 1996     1     32     2     31     2.7%     0.47 [0.17, 76]       Moore 1906     1     32     2     31     2.5%     0.48 [0.05, 507]       Peck 2004     4     14     5     31<[1.0%     0.74 [0.25, 2.16]	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]	
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Kompan 2004     0     27     1     25     1.3%     0.31     0.01     7.7.85       Moore 1906     1     22     2     1     2.3%     0.43     0.05     5.07       Nguyen 2008     6     1.4     6     1.4     1.75%     1.00     0.43     2.55     0.74       Peck 2004     4     1.4     5     1.3     1.0%     0.74     0.25     5.07       Pupeliti: 2000     1     1.5     1.8     3.2%     0.33     0.04, 2.45     0.74     0.25     1.0%       Schneded (793)     0     1.6     0.74     0.02, 1.0%     0.35     0.04, 2.45     0.0%       Watters 1997     0     1.3     0     1.6     Not estimable     0.59     0.25     0.38     0.38     0.38     0.38     0.38     0.38     0.38     0.38     0.34     0.59     0.50     0.55     0.50     0.50     0.50     0.50     0.50     0.50     0.50     0.50     0.50     0.50     0.50	Chuntrasakul 1998	1	21	3	17	2.7%	0.27 [0.03, 2.37]	
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Npuren     2008     6     14     6     14     17.5%     100 [0.43, 2.35]       Peak: 2004     4     14     5     13     10.0%     0.74 [0.25, 2.16]       Pupelin: 2000     1     11     5     18     3.7%     0.33 [0.04, 2.45]       Pupelin: 2001     1     30     7     30     3.1%     0.14 [0.02, 106]       Schroeder 1991     0     16     0     16     Not estimable       Watters 1997     0     13     0     15     Not estimable       Total events     16     35     35     39.35, 0.38]     Image: Schroeder 19.35, 0.98]	Kompan 2004	0	27	1	25	1.3%	0.31 [0.01, 7.26]	
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Pupelici 2000     1     11     5     18     32%     0.33 [0.04, 2.45]       Pupelici 2001     1     30     7     30     31%     0.14 [0.02, 1.66]       Schroeder 1991     0     15     0     16     Not estimable       Waters 1997     0     13     0     15     Not estimable       Schroeder 1991     0     15     0.16 estimable     Total events       Total events     16     35     Schroeder 1991     0	Nguyen 2008	6	14	6	14	17.5%	1.00 [0.43, 2.35]	
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Watters 1997     0     13     0     15     Notestmable       Stabilation (95% C0)     246     247     48.6%     0.59 [0.35, 0.98]     Image: Comparison of the comparison o	Pupelis 2001	1	30	7	30	3.1%	0.14 [0.02, 1.09]	
Subtorlat (95% CD) 246 247 48.6% 0.59 [0.35, 0.98] Total events 16 35 Total events 16 35 Total events - 0.000 CD = 0.800, P= 0%	Schroeder 1991	0	16	0	16		Not estimable	
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14 monomity Torize 0.00 Chiller 5.24 H = 9 (P = 0.80); P = 0%	Subtotal (95% CI)		246		247	48.6%	0.59 [0.35, 0.98]	( 🔶 )
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	Holorogeneily Toul - 0.0	0.01.2			0); I <sup>2</sup> = 0	%		
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	Early	EN	Delayed/No	ne EN		Risk Ratio	Risk Ratio
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Test for o	werall effect Z =	2.03 (P	= 0.04)	c= 9 (P = 0.8	ο); r <sup>2</sup> = 0	76		



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  - 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.
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- 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,
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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.







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



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### Assorted loose ends

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- 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.



Full economic analyses based on large-scale Monte Carlo simulations of stochastic cost models demonstrate clinical benefits can be achieved whilst at the same time reducing costs.

- EN US\$14,462 (95% CI \$5,464 to \$23,669) savings per patient treated
- ¥ 9,000 RMB per patient savings using local costs of ICU care www.EvidenceBased.net/talks

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  - There is no robust evidence to mandate specific rates or goals.
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- 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.