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

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Summary of this talk

- Review the most recent clinical evidence on the topic.
- Discuss physiological ramifications.
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- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.

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Chiarelli 1990	0	10	0	10		Not estimable
Chuntrasakul 1996	1	21	3	17	2.7%	0.27 [0.03, 2.37]
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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]
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Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
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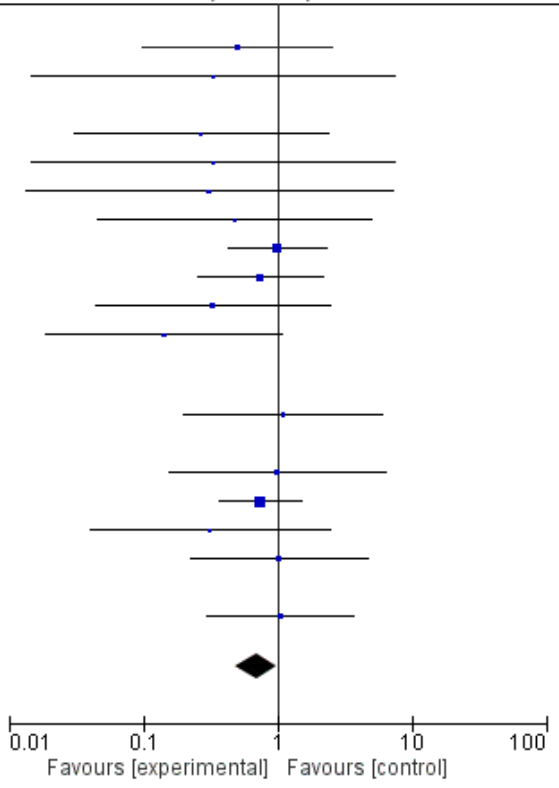
Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
Total events	41		66			

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%



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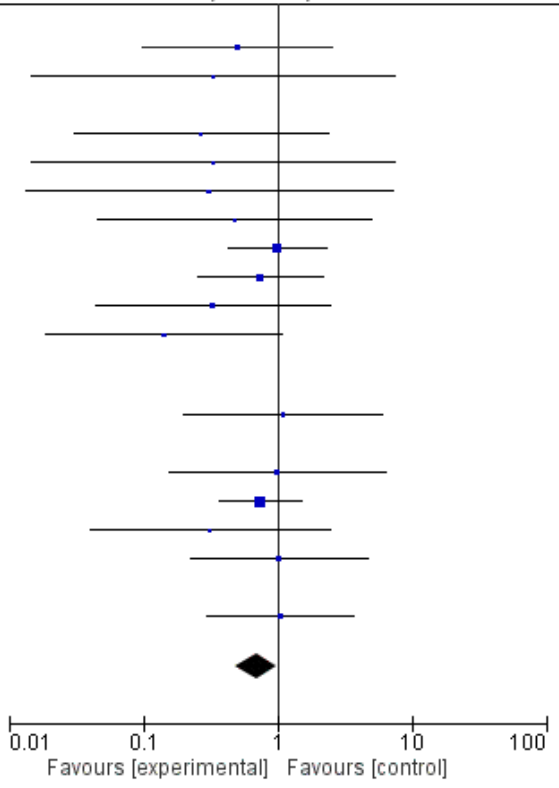

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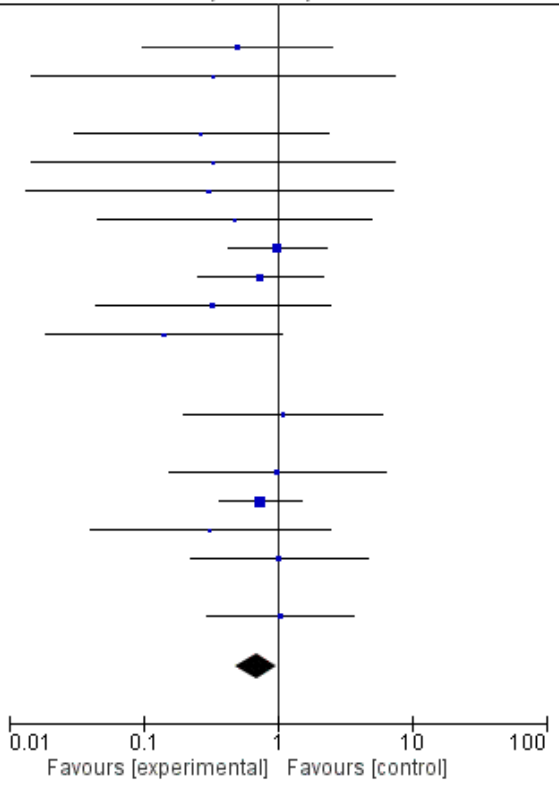

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Recommends early EN within 24 to 48 h of ICU admission

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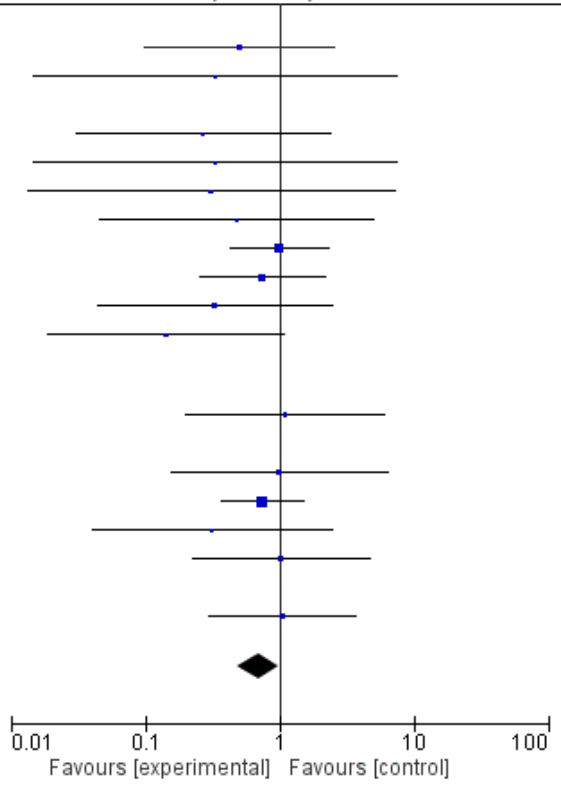

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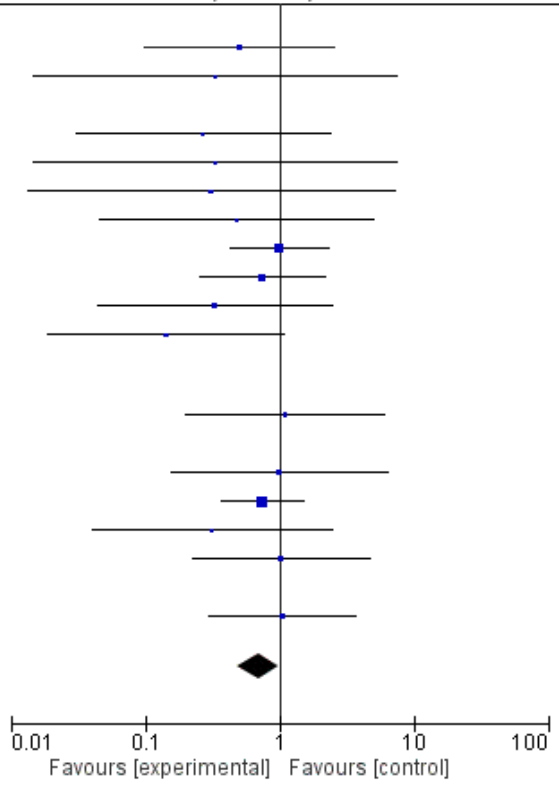
< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]
	Total (95% CI)		**483**		**483**	**100.0%**	**0.70 [0.49, 1.00]**
	Total events	41		66			

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%

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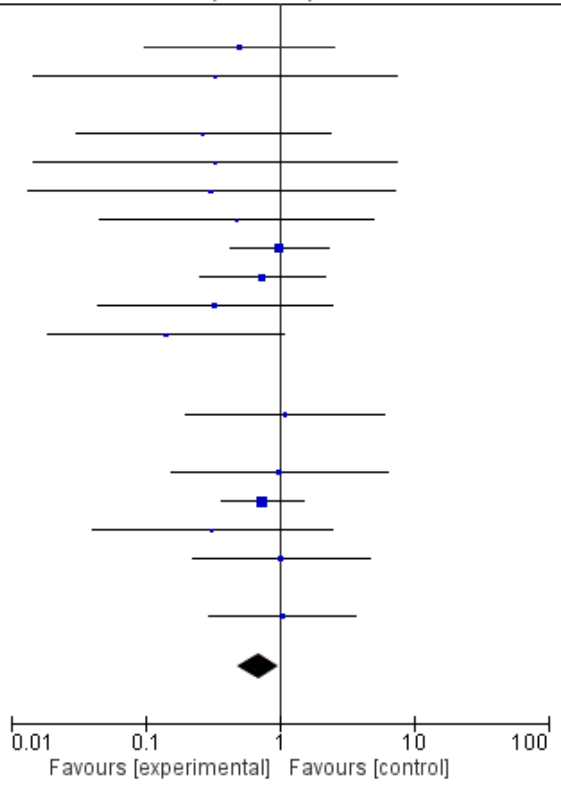

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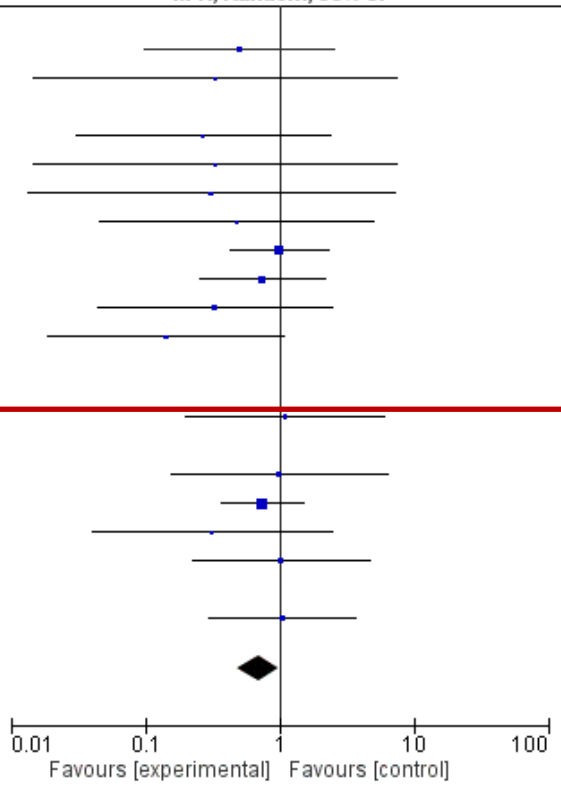

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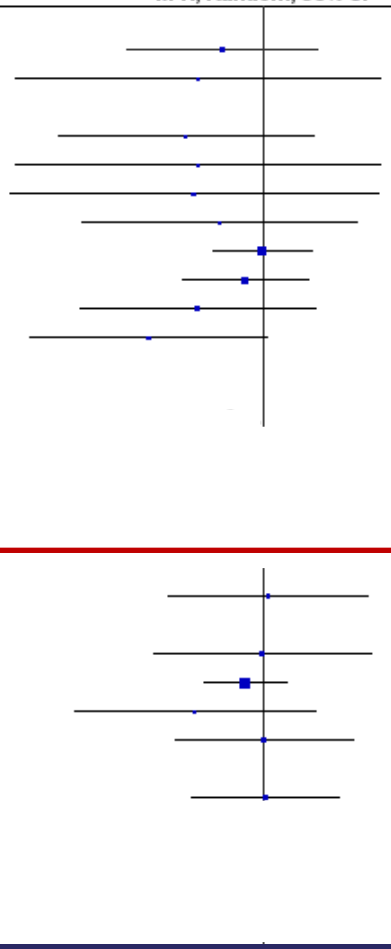

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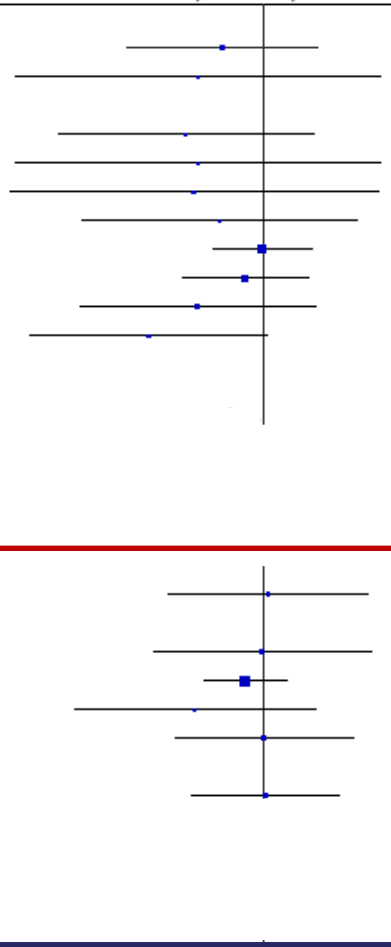

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	Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
	Total events	16		35			
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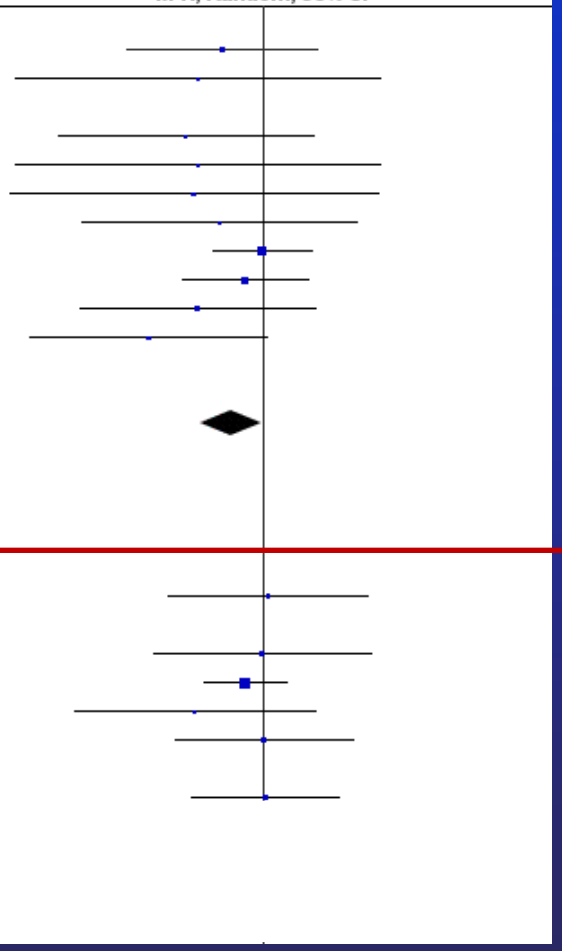

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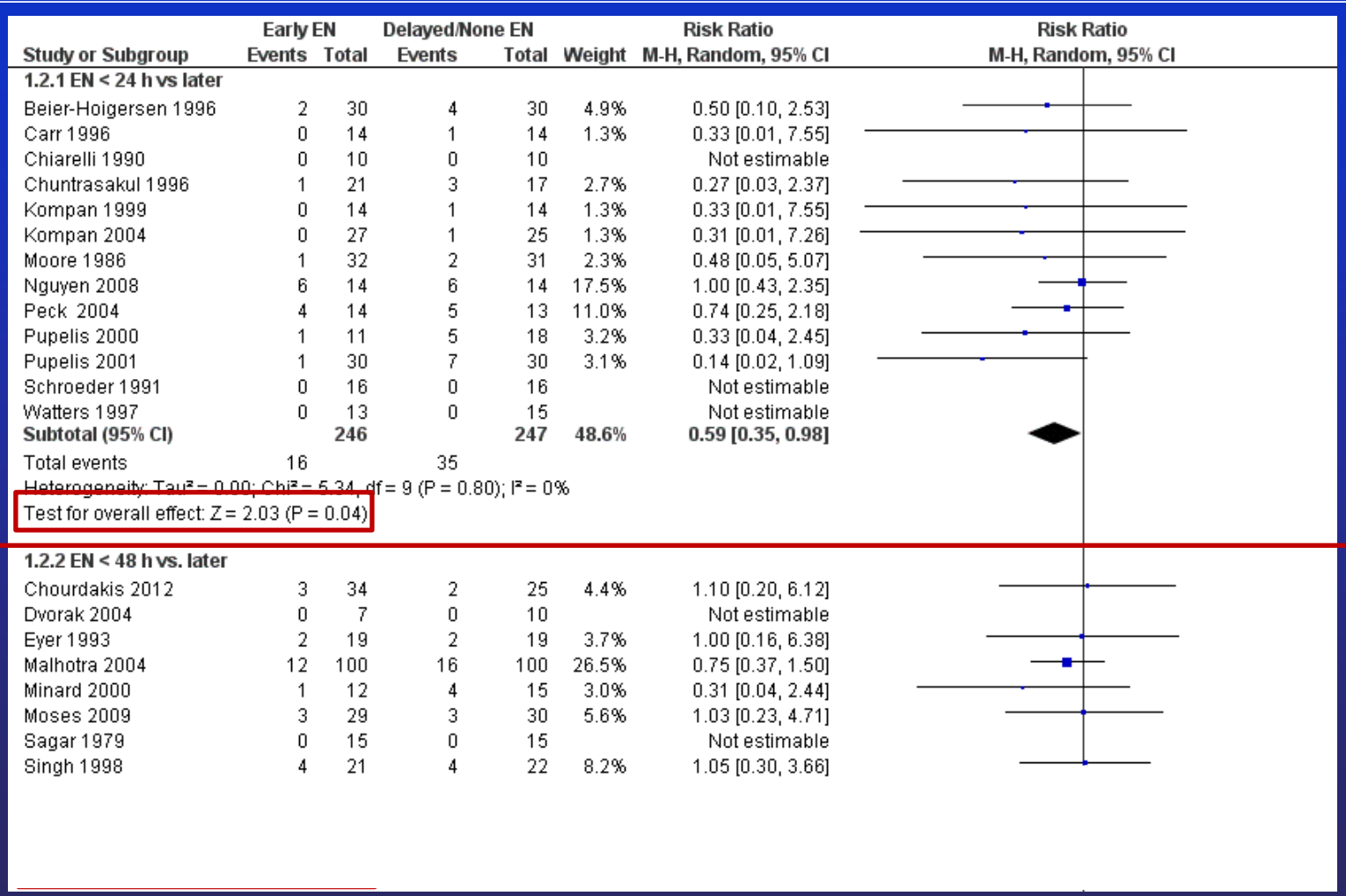

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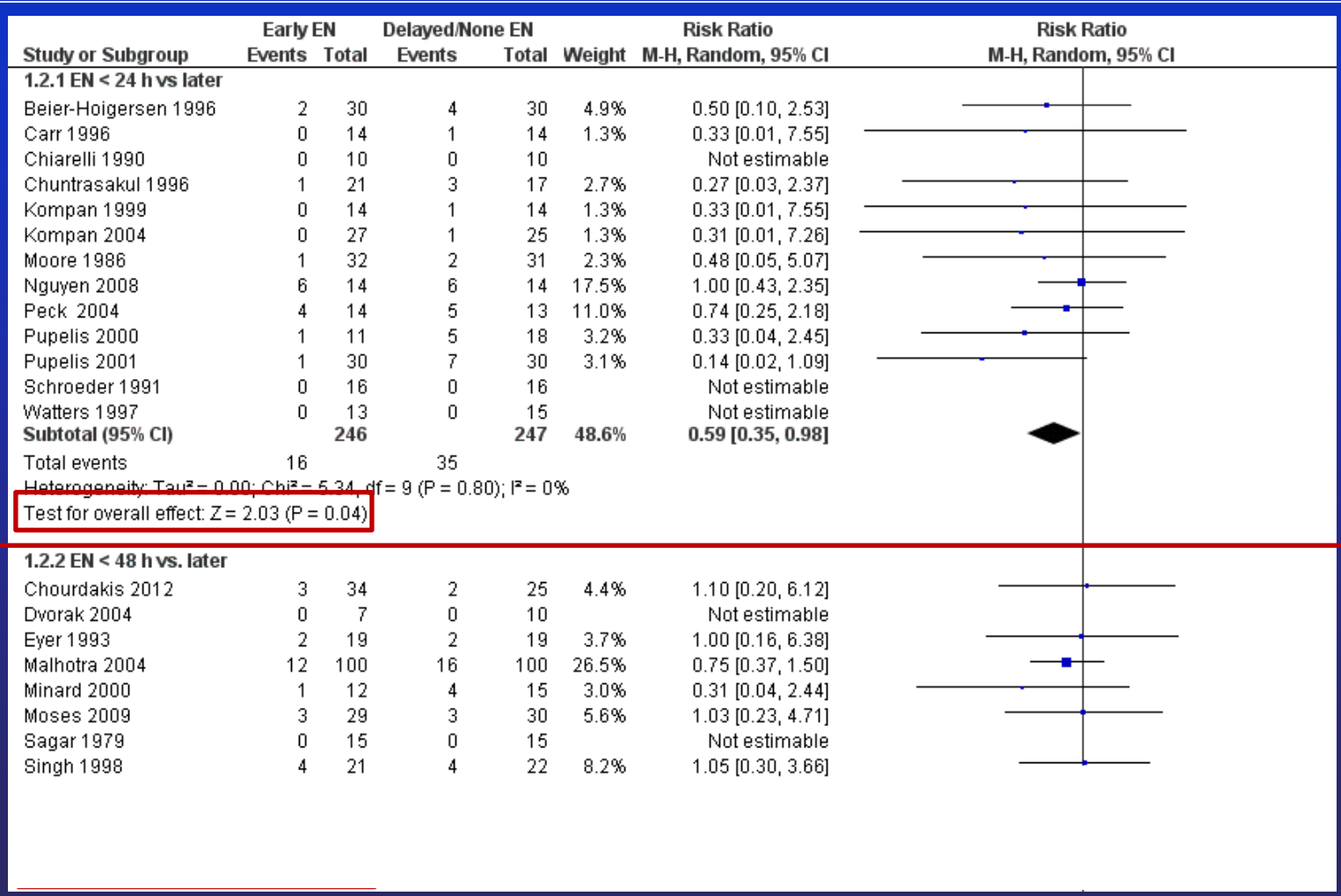

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< 31h	Eyer 1993	2	19	2	19	3.7%	1.00 [0.16, 6.38]
< 48h	Malhotra 2004	12	100	16	100	26.5%	0.75 [0.37, 1.50]
< 60h	Minard 2000	1	12	4	15	3.0%	0.31 [0.04, 2.44]
< 48h	Moses 2009	3	29	3	30	5.6%	1.03 [0.23, 4.71]
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< 48h	Singh 1998	4	21	4	22	8.2%	1.05 [0.30, 3.66]

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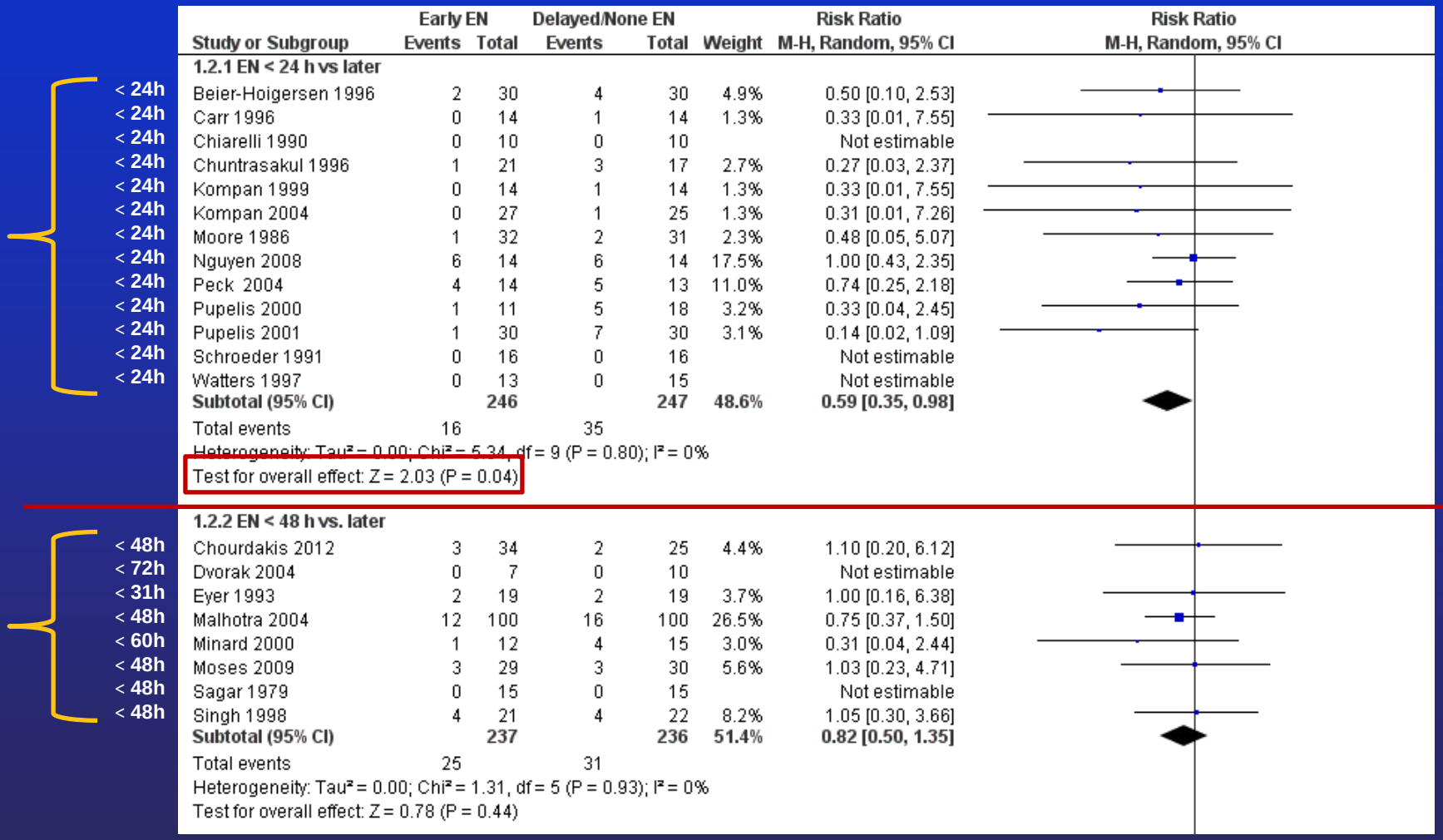

	Study or Subgroup	Early EN Events	Early EN Total	Delayed/None EN Events	Delayed/None EN Total	Weight	Risk Ratio M-H, Random, 95% CI
	1.2.1 EN < 24 h vs later						
< 24h	Beier-Hoigersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
< 24h	Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
< 24h	Chiarelli 1990	0	10	0	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]
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< 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]
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	Total events	25		31			
	Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 5 (P = 0.93); I² = 0%						
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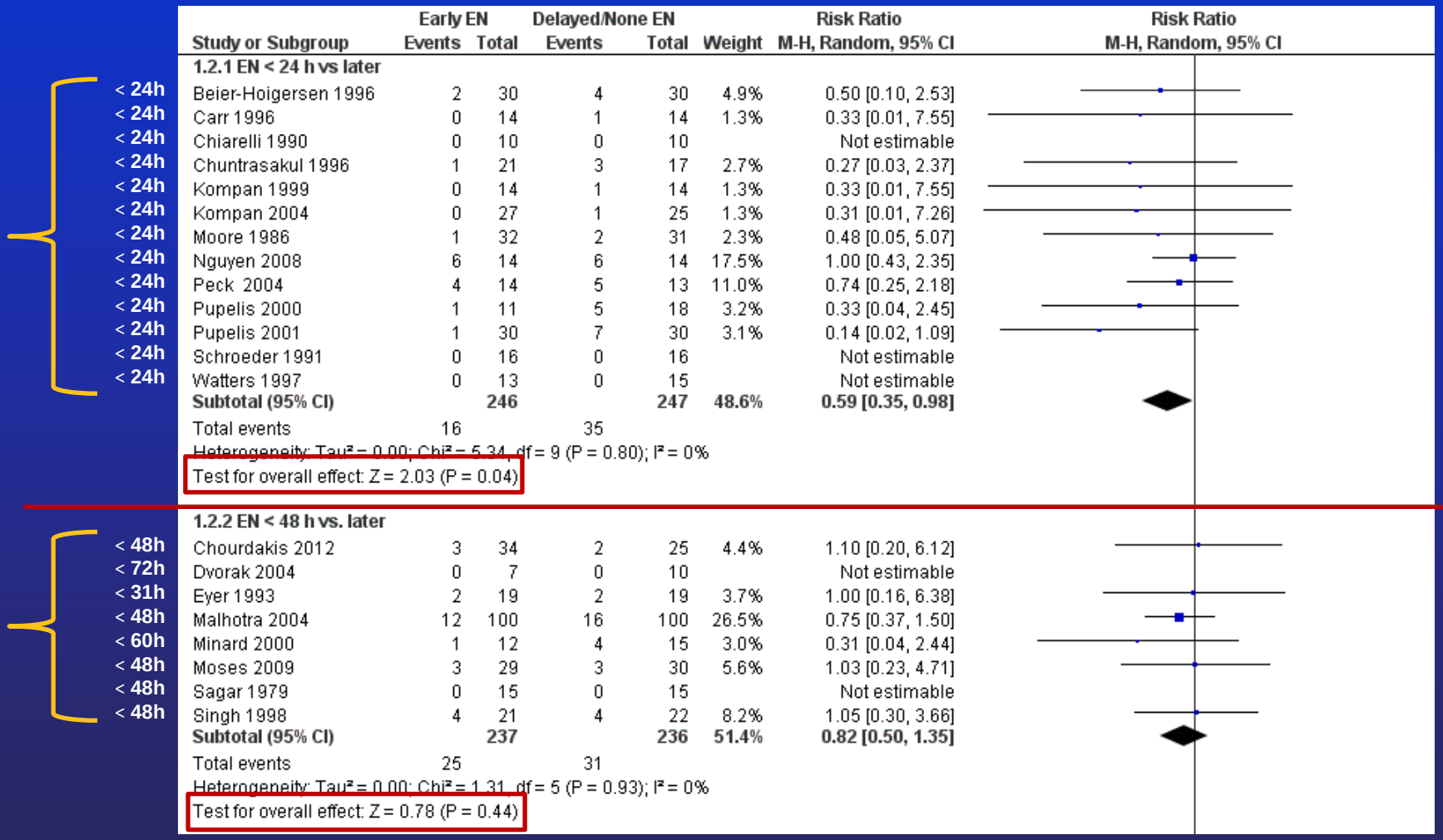

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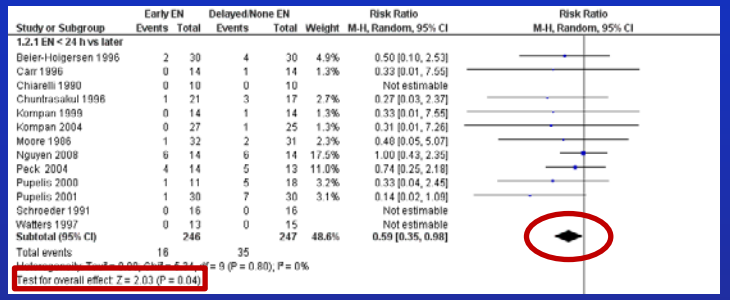

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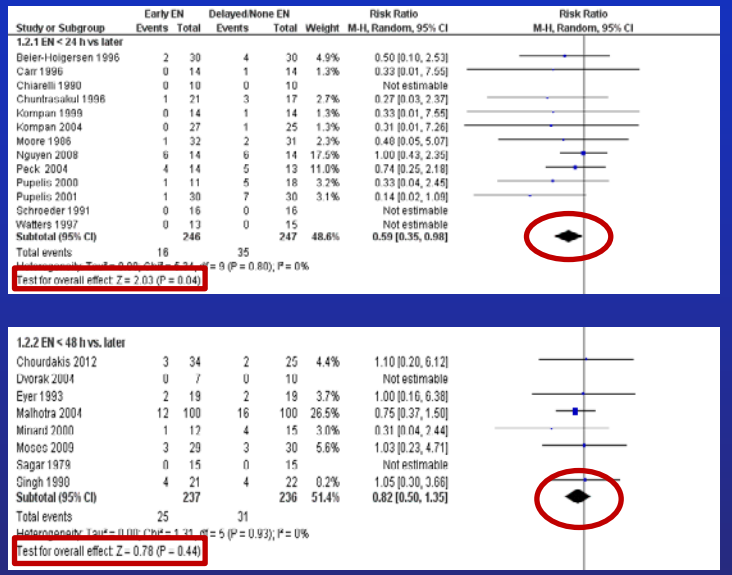

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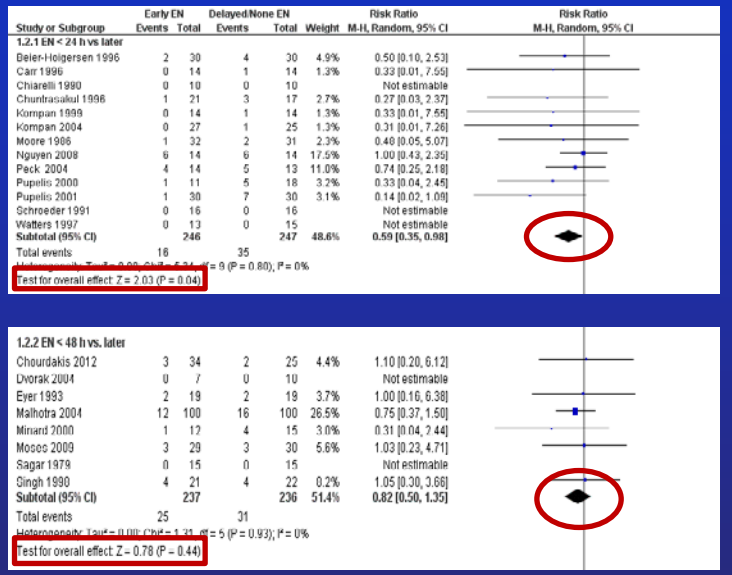

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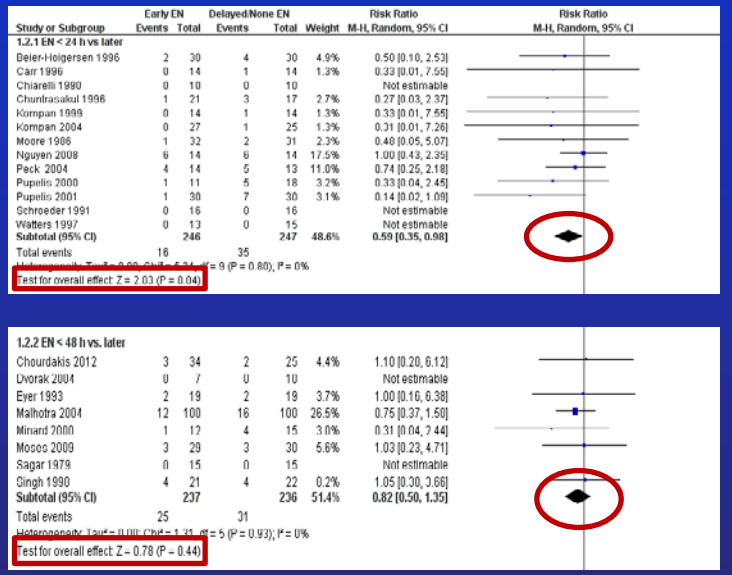

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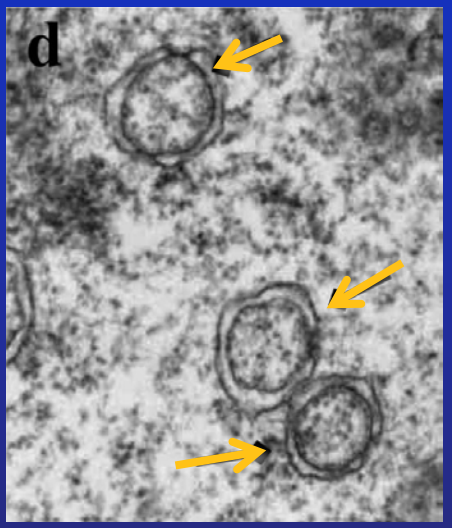

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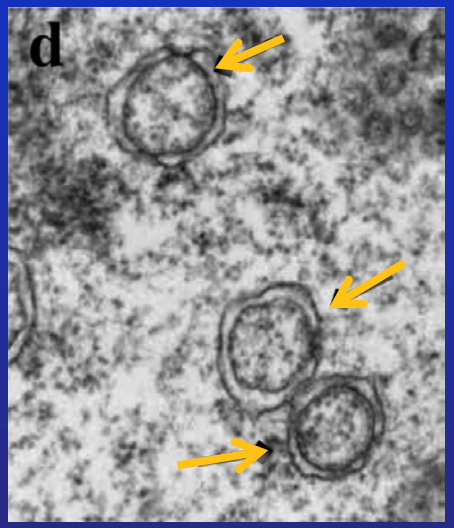

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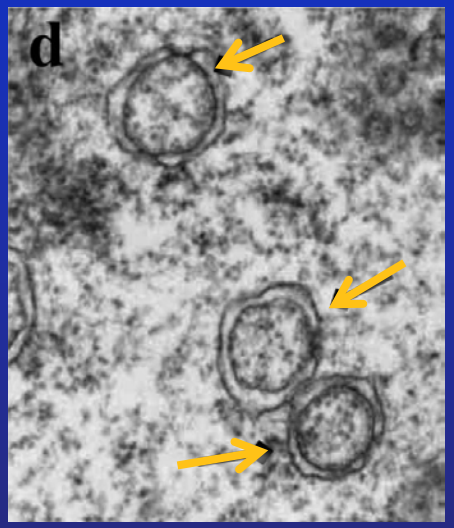

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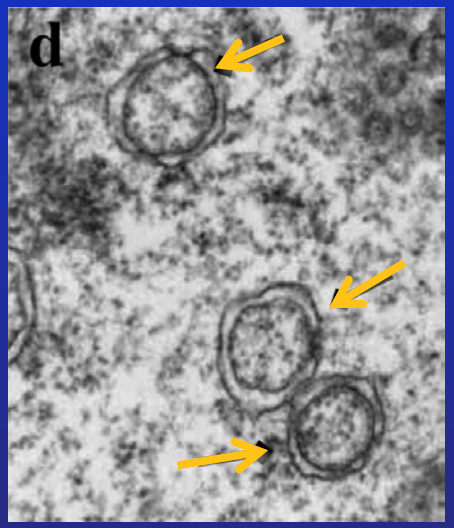

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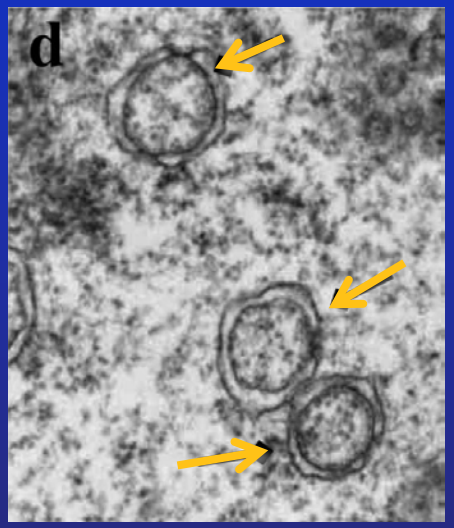

"In nutrient deprivation, autophagy activates bulk protein (non-selective) degradation to harvest amino acids as a fuel for ATP production through the tricarboxylic acid (TCA) cycle."

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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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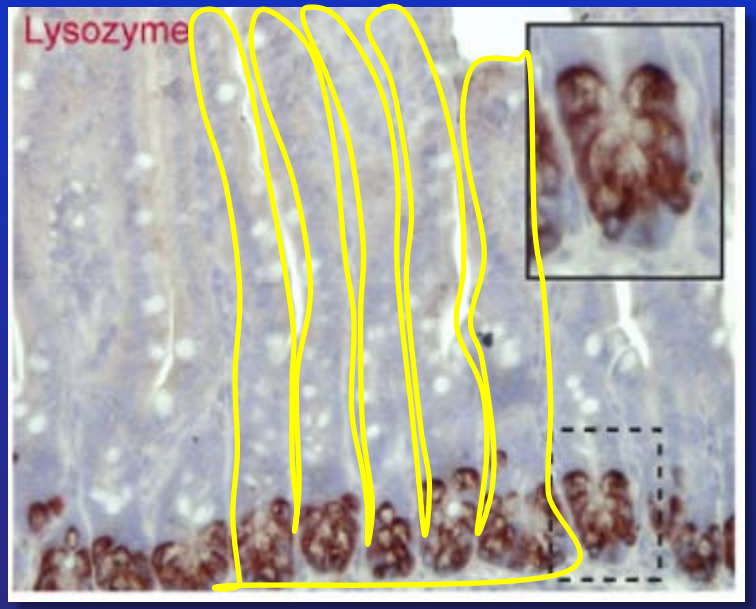

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- They are the main producers of antimicrobial proteins in the gut.
- Create and secrete granules containing antimicrobial peptides.
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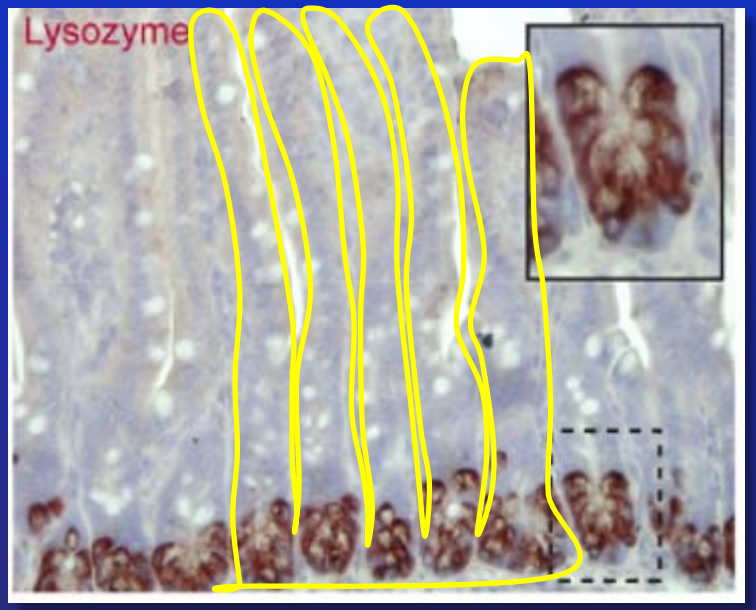

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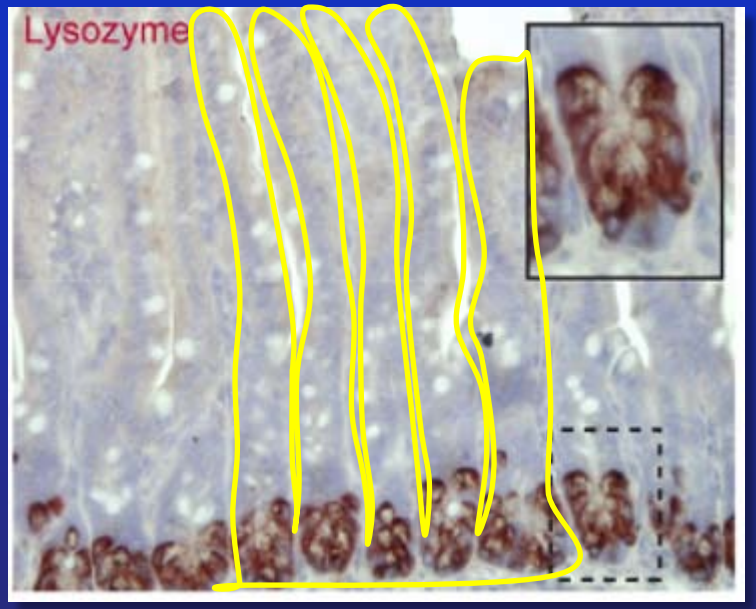

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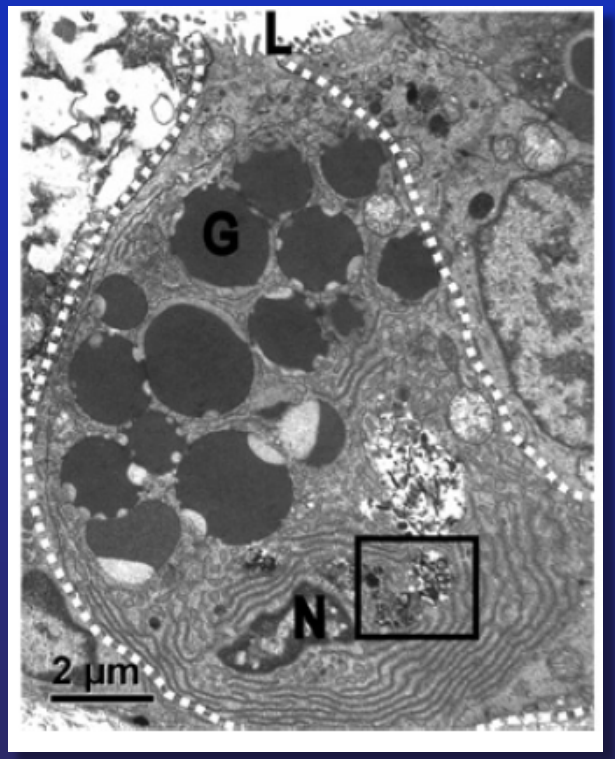

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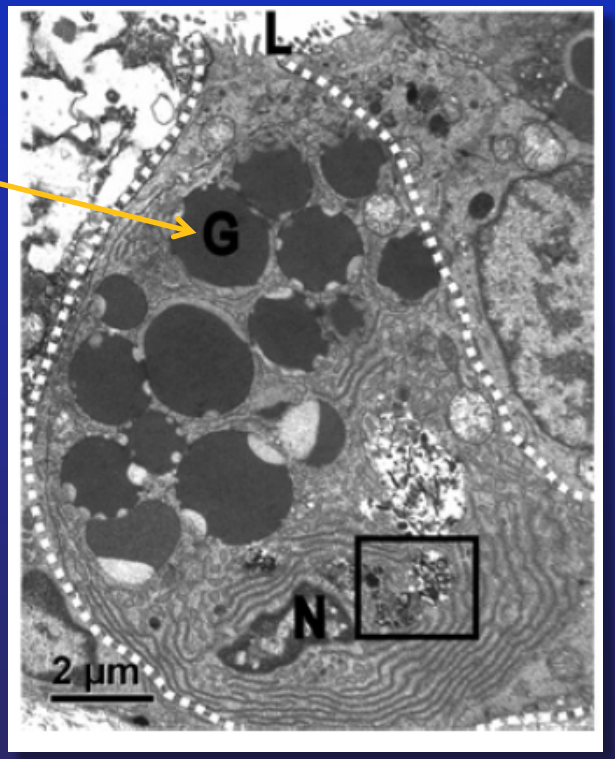

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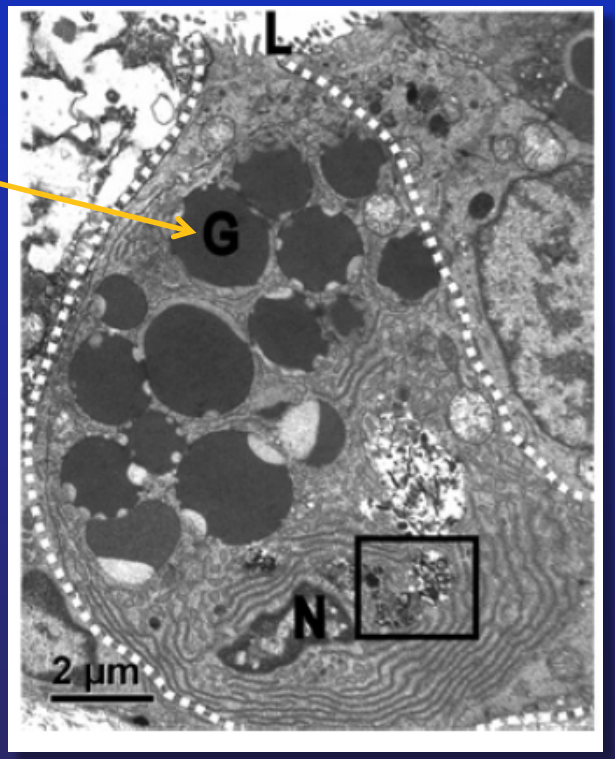

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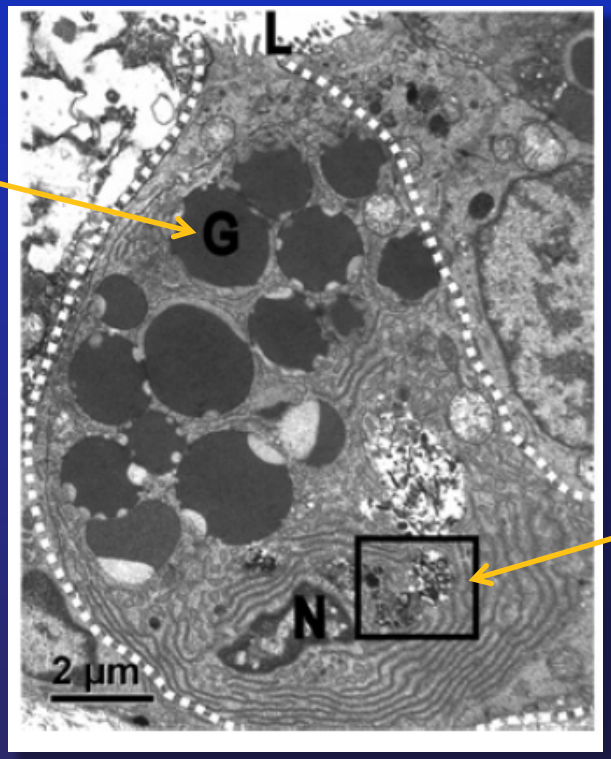

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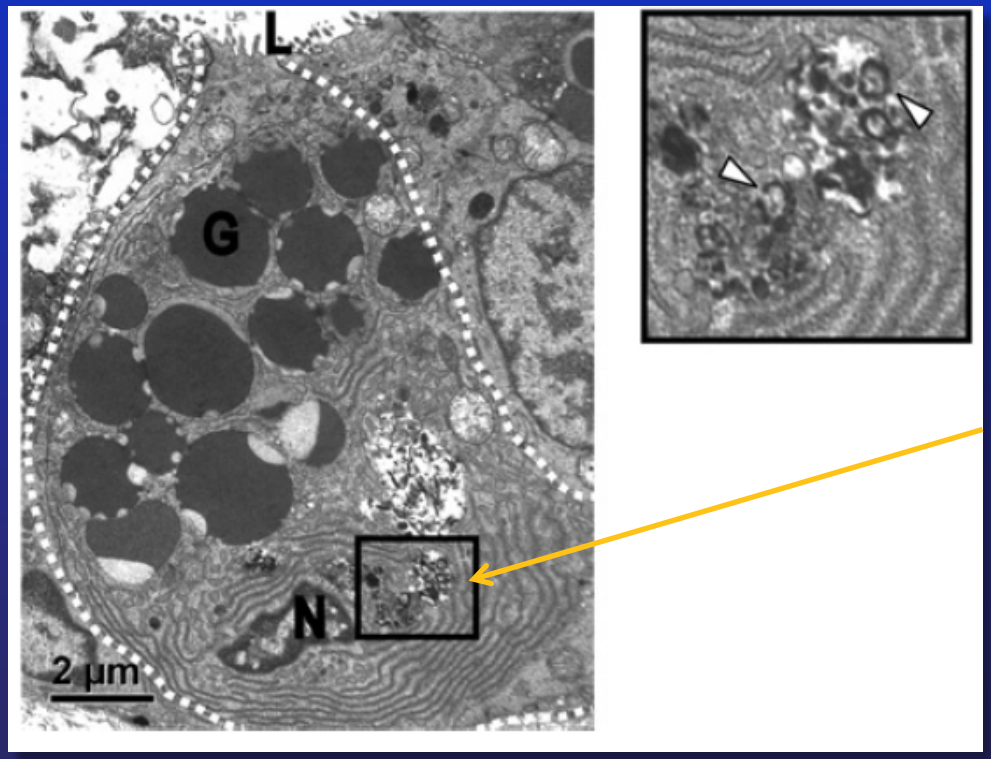

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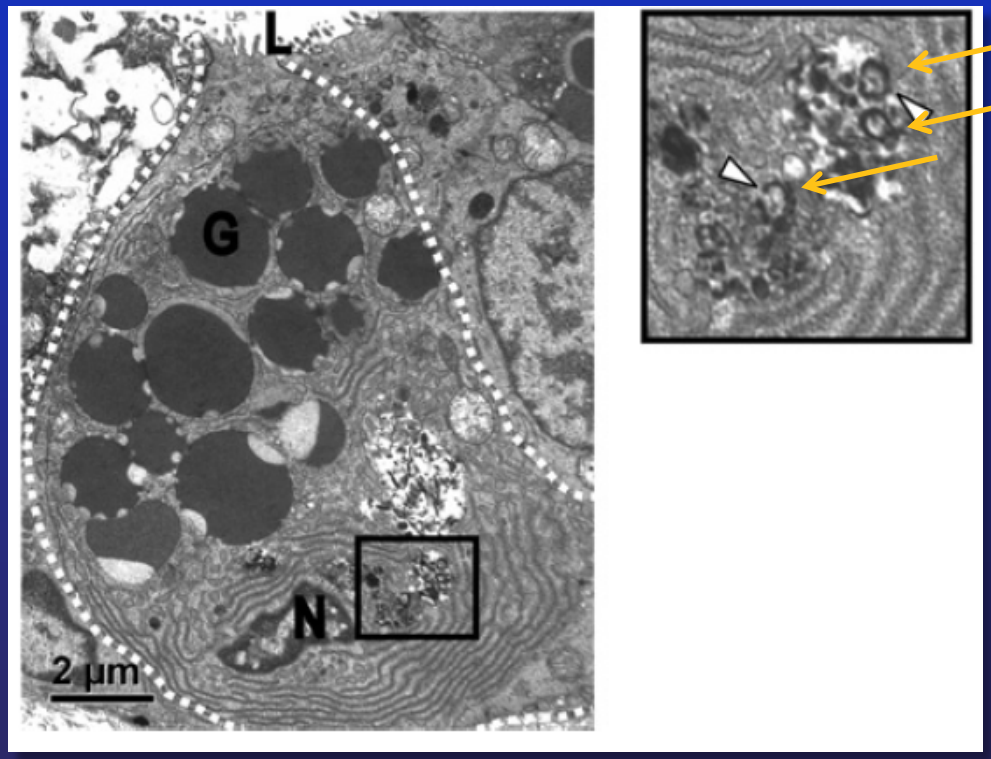

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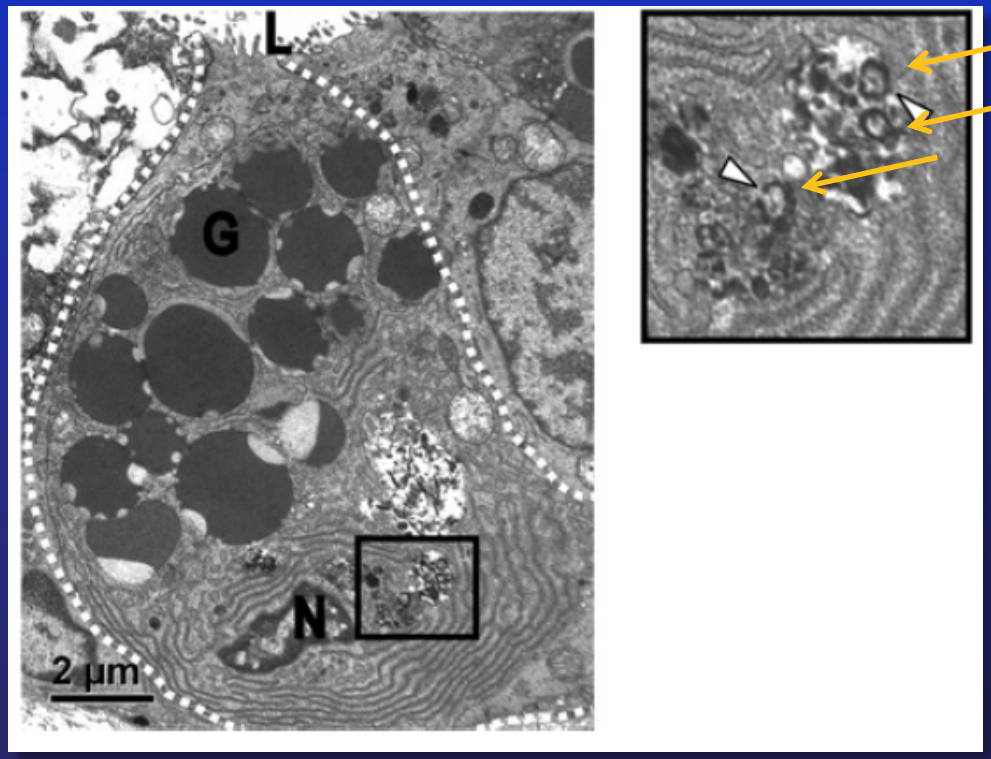

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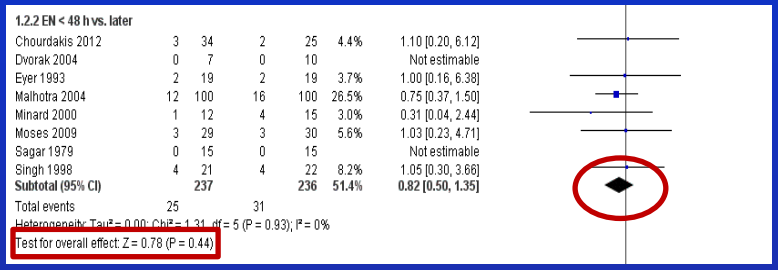

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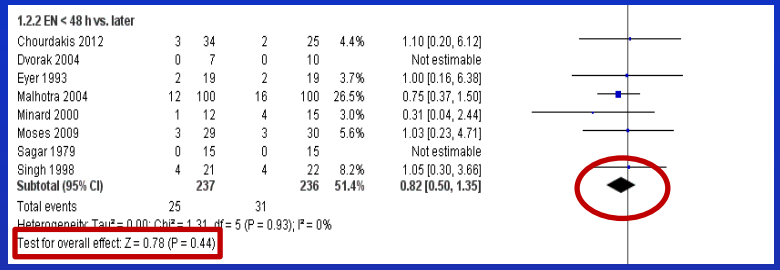

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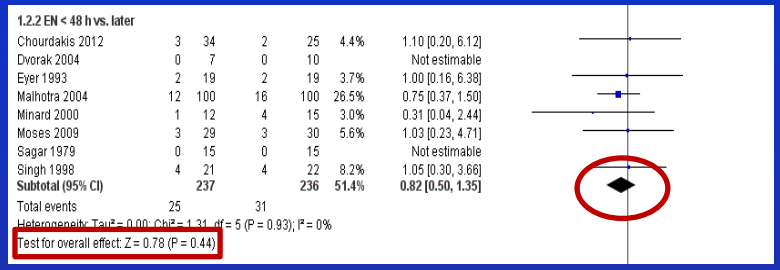

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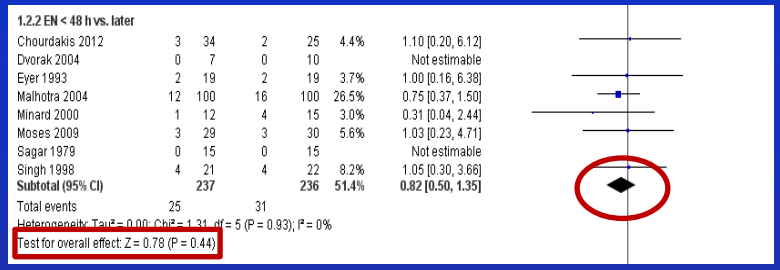

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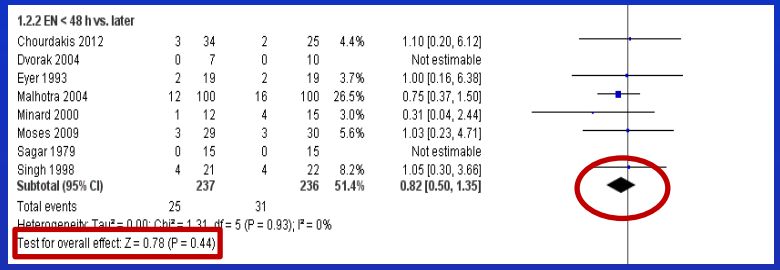

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  - and perhaps even brain function (delirium, long-term cognitive impairment).

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.

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- 2016 SCCM/ASPEN guideline
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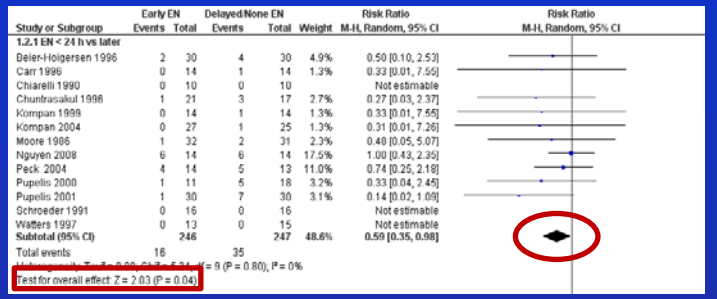

Study or Subgroup	Early EN Events	Total	Delayed/None EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 EN < 24 h vs later						
Beier-Holgersen 1996	2	30	4	30	4.9%	0.50 [0.10, 2.53]
Carr 1996	0	14	1	14	1.3%	0.33 [0.01, 7.55]
Chiarelli 1990	0	10	0	10		Not estimable
Chuntrasakul 1998	1	21	3	17	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
Subtotal (95% CI)		**246**		**247**	**48.6%**	**0.59 [0.35, 0.98]**
Total events	16		35			
						= 9 (P = 0.80), P = 0%
Test for overall effect: Z = 2.03 (P = 0.04)						

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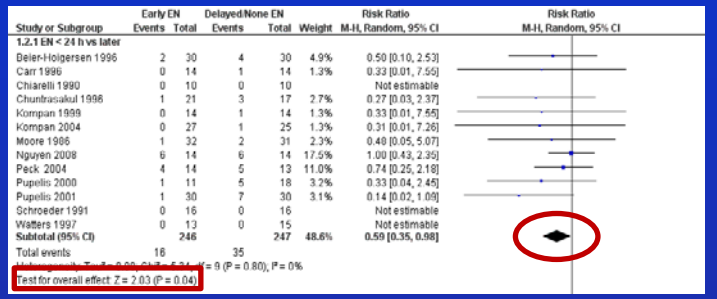

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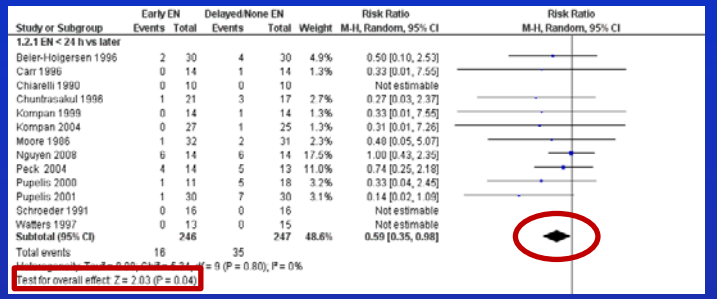

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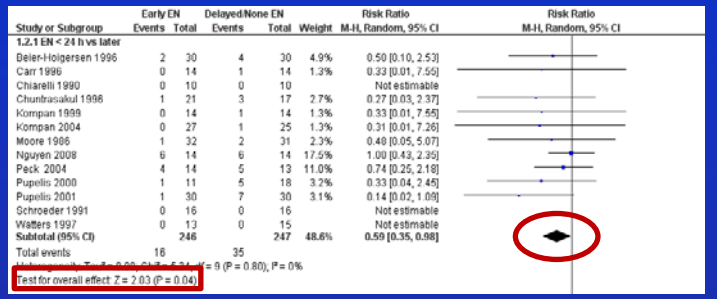

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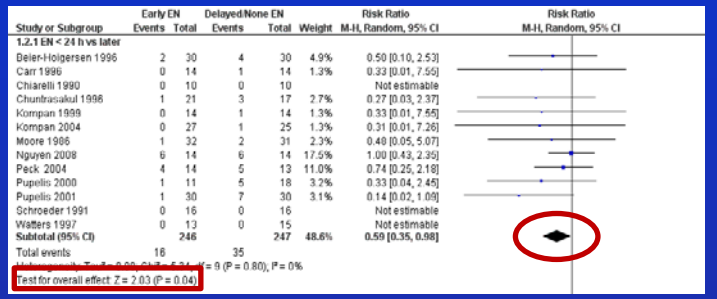

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  - *In a mouse model of TBI, partially inhibited autophagy leading to improvements in behavioural and histological outcomes.*

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

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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.

Questions?

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

Assorted loose ends

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  - There is no robust evidence to mandate specific rates or goals.
  - In general, start slow and achieve reasonable goals within 3 to 7 days.

Economic Analysis: Early EN reduces costs

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

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  - 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.