Suplementação em humanos doentes graves.

André Nunes

XVII Congresso CBNA PET
DIAS 16 E 17
MAIO | 2018
Local: Expo D Pedro
Campinas, SP

Conflito de interesses.

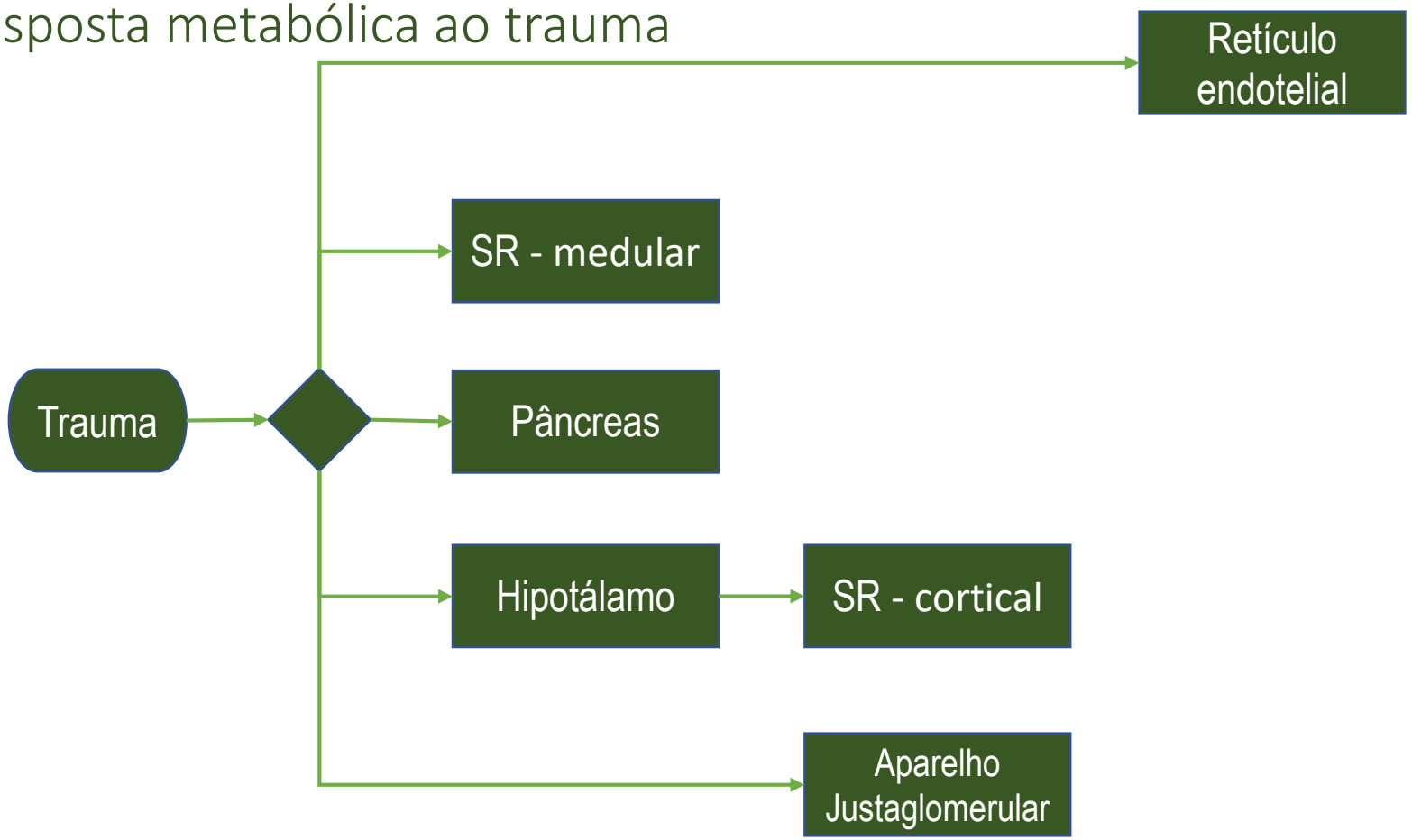


Pauta

- Resposta orgânica ao trauma.
- Reposição e suplementação.
- Associação e relação de causa e efeito.
- Revisão crítica da literatura em humanos:
  - Suplementação calórica.
  - Imunonutrição.
  - Probióticos, Simbióticos.

Introdução

Resposta metabólica ao trauma



Pressão arterial
Glicemia

Volemia
Perfusão

Inflamação

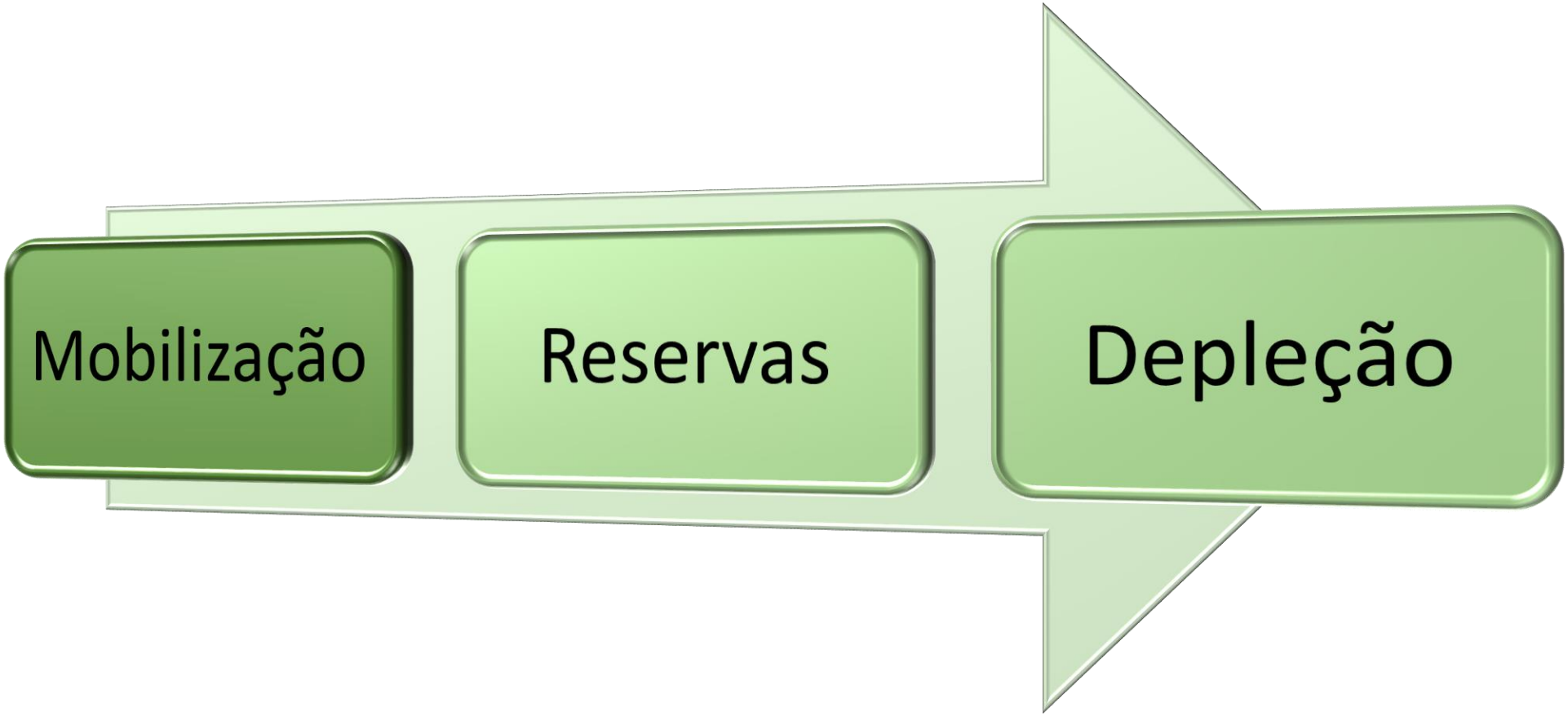
Introdução

Resposta metabólica ao trauma

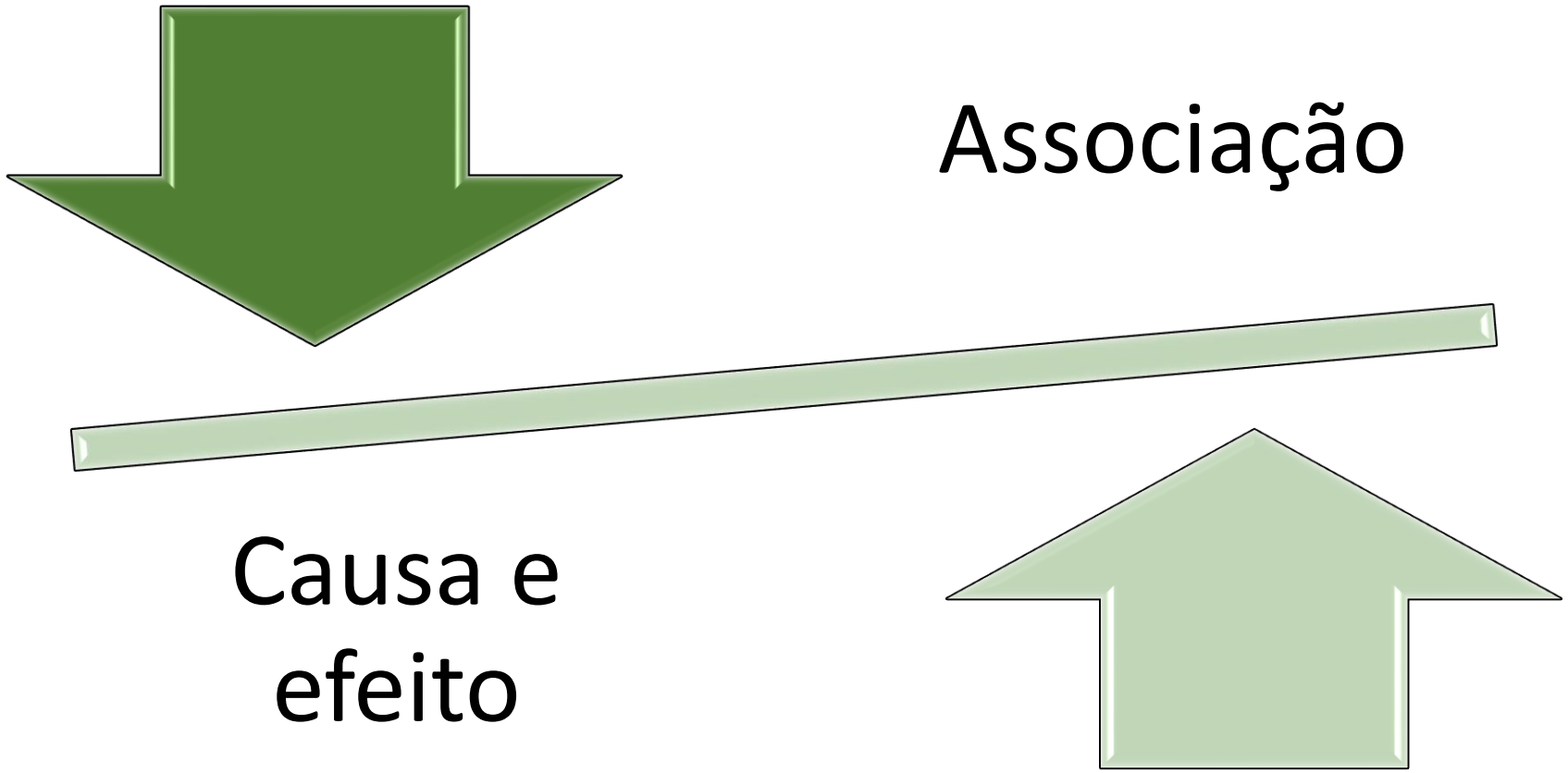
Hemodinâmica	Humoral	Metabólica
Choque descompensado: pressão arterial baixa, hipoperfusão orgânica.	Adrenalina Noradrenalina Glucagon ADH	Catabolismo proteico Resistência hepática a insulina Neoglicogênese Glicogenólise Hiperglicemia Retenção de água Hipometabolismo
Choque compensado: pressão arterial normal, hipoperfusão orgânica.	Cortisol Renina Angiotensina Aldosterona	Catabolismo proteico Mobilização de lipídeos Resistência periférica a insulina Retenção de água e sal Hipometbolismo
Perfusão orgânica restabelecida.	Interleucinas Prostaglandinas Redução da conversão periférica t4-t3	Catabolismo proteico Mobilização de lipídeos Resistência periférica a insulina Hipermetabolismo (?)

Introdução

Reposição e suplementação

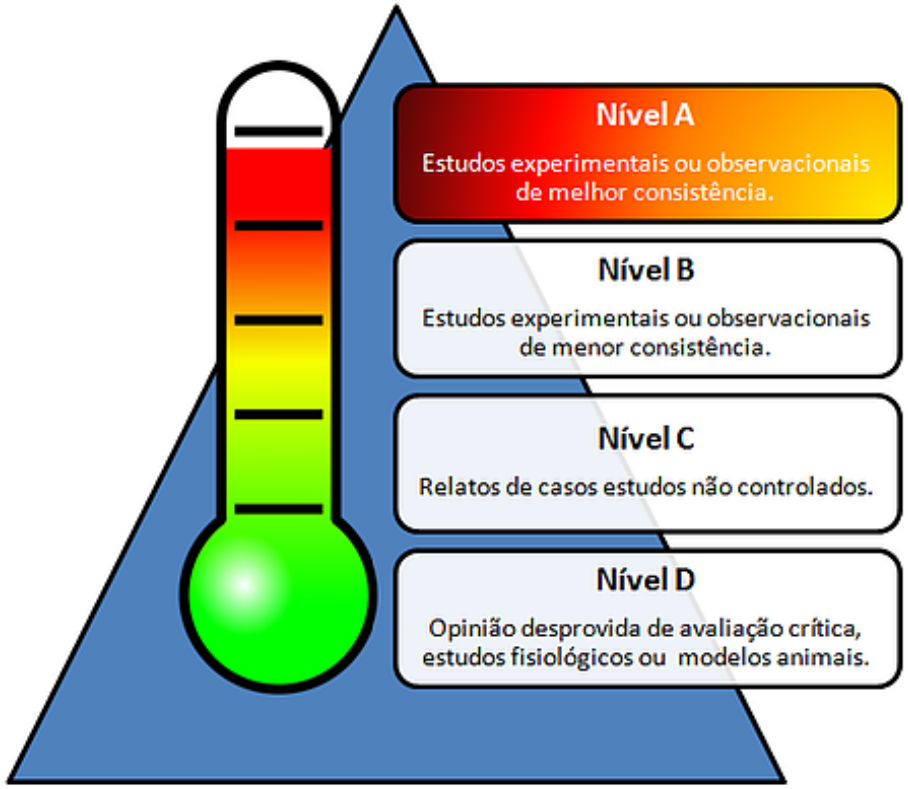


Introdução



Critérios de Hill (1965).

1. Força da associação: quanto mais forte uma associação, mais provável que seja causal. A força da associação é medida pelo risco relativo ou pelo odds ratio
2. Consistência: a relação deve ser condizente com os achados de outros estudos
3. Especificidade: exposição específica causa a doença
4. Temporalidade: causa deve ser anterior à doença
5. Gradiente biológico (efeito dose-resposta): deve ser em gradiente, proporcional
6. Plausibilidade biológica: A associação deve ter uma explicação plausível, concordante com o nível atual de conhecimento do processo patológico
7. Coerência: os achados devem seguir o paradigma da ciência atual
8. Evidências experimentais: Mudanças na exposição mudam o padrão da doença
9. Analogia: com outra doença ou com outra exposição



Hierarquia da Evidência



COOK et al., 1992; ECCLES; FREEMANTLE; MASON, 1998

Medicina baseada em evidências

Suplementação calórica

Asia Pac J Clin Nutr 2017;26(1):11-19 11

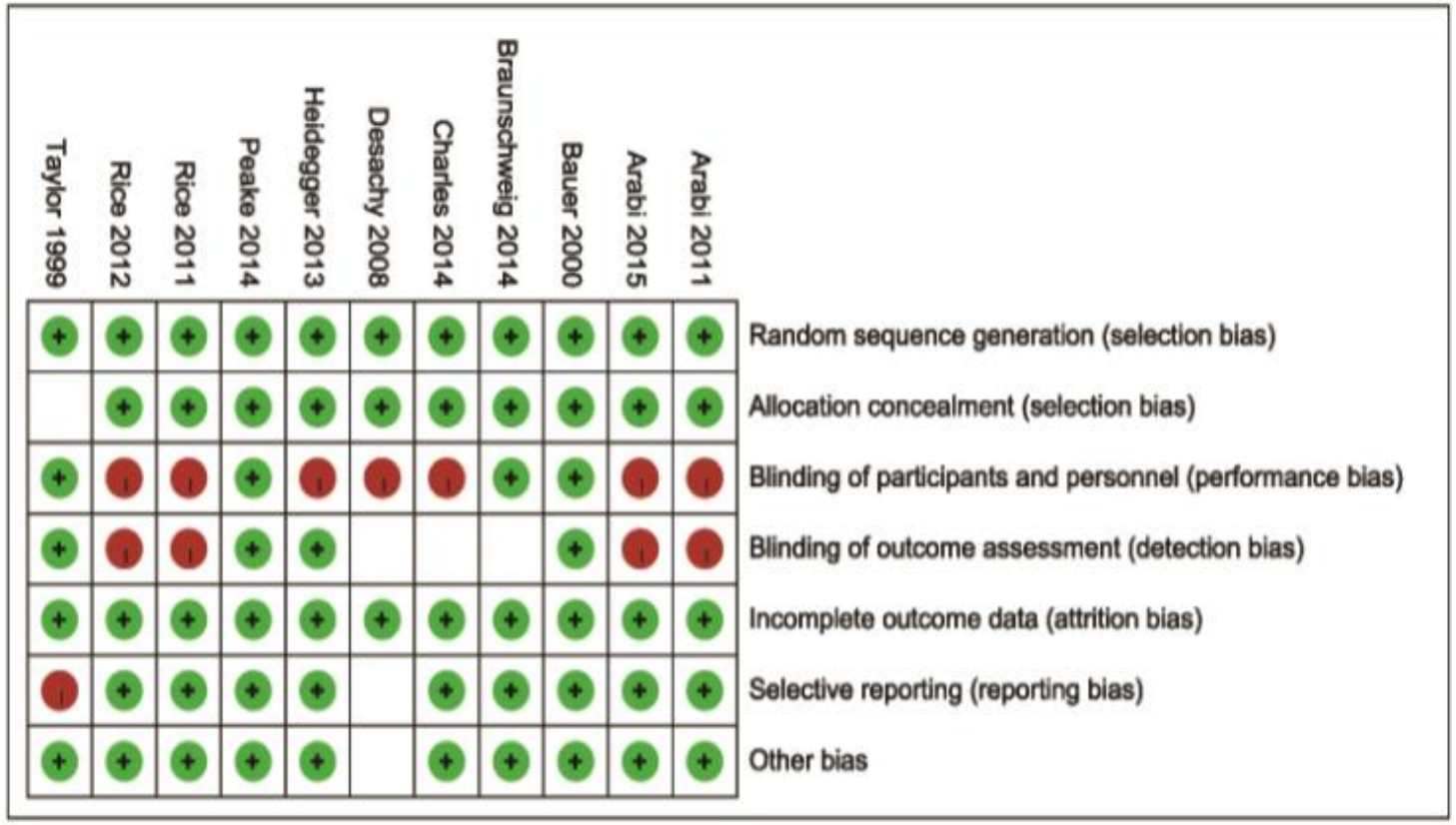
Original Article

Initial energy supplementation in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized controlled trials

Feng Tian MD[1], Xuejin Gao MS[2], Chao Wu MD[1], Li Zhang MD[1], Xianfeng Xia MD[1], Xinying Wang MD[1]

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[2]*Department of General Surgery, Jinling Hospital, South Medical University, Guangdong Province, China*

Bias


Taylor 1999
Rice 2012
Rice 2011
Peake 2014
Heidegger 2013
Desachy 2008
Charles 2014
Braunschweig 2014
Bauer 2000
Arabi 2015
Arabi 2011
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Trabalhos

Table 1. Characteristics of the enrolled studies

Study	NO. randomized		Characteristics of patients	Mean age (SD)		Duration of intervention
	LE	HE		LE	HE	
Arabi et al	120	120	>18 years old ICU >48 hours	50.3 (21.3)	51.9 (22.1)	1-7 day
Arabi et al	447	445	>18 years old ICU >72 hours EN within 48 hours of ICU admission	50.2 (19.5)	50.9 (19.4)	14 day
Bauer et al	60	60	>18 years old ICU >48 hours	55 (18)	53 (18)	1-7 day
Braunschweig et al	38	40	medical or surgical ICU >18 years old Within 24 hours of ALI	58.6 (16.2)	52.5 (17.1)	1-20 day
Charles et al	41	42	>18 years old Artificial Nutrition >48 h ICU >48 hours	50.4 (17.9)	53.4 (17.5)	10-12 day
Desachy et al	50	50	Medical or surgical ICU >18 years old	64 (13)	58 (19)	1-5 day
Heidegger et al	153	152	ICU>5 day Survive>7 day	60 (16)	61 (16)	4-8 day
Peake et al	55	57	>18 years old Enteral nutrition ≥ 2 days Mechanical ventilation	56.5 (16.1)	56.4 (16.8)	10 day
Rice et al	98	102	ICU admission Mechanical ventilation > 72 hours	53 (19)	54 (17)	0-6 day
Rice et al	508	492	ICU admission ALI <48 hours Mechanical ventilation >72 hours	52 (17)	52 (6)	1-6 day
Taylor et al	41	41	Patients of head injury necessitating mechanical ventilation Glasgow Coma Scale >3 >10 years old	28	34	1-7 day

LE: low energy; HE: high energy; ICU: intensive care unit; ALI: acute lung injury; SD: standard deviation.

Suplementação calórica
características dos trabalhos

Table 2. Characteristics of the enrolled studies continued

Mean of APACHE Ⅱ/Ⅲ score (SD)		Regimen of nutrition		Mean daily percentage of caloric goal (%)		Mean daily protein intake (g)	
LE	HE	LE	HE	LE	HE	LE	HE
25.2 (7.5)	25.3 (8.2)	EN	EN	59.0	71.4	47.5	43.6
21.0 (7.9)	21.0 (8.2)	EN	EN	46	71	57	60
N/A	N/A	EN	EN+PN	46.4	90.9	N/A	N/A
27.7 (7.9)	23.4 (9.3)	EN	EN	55.4	84.7	60.4	82
16.6(0.9)	17.3 (0.8)	EN	EN	40.5	73	86	83
40 (11)‡	42 (17)‡	EN	EN	76	95	N/A	N/A
23 (7)	22 (7)	EN	EN+PN	77	103	61.8	89.8
22 (8.9)	23 (9.1)	EN	EN	72	102	70	74
26.9 (8.1)	26.9 (6.6)	EN	EN	15	74.8	10.9	54.4
92 (28)†	90 (27)†	EN	EN	25	80	N/A	N/A
14	14	EN	EN	36.8	59.2	37.9%§	68.7%§

LE: low energy; HE: high energy; ICU: intensive care unit; ALI: acute lung injury; SD: standard deviation.
‡Mean of SAPS Ⅱ, SAPS Ⅱ: Simplified Acute Physiology Score Ⅱ.
†Mean of APACHE Ⅲ score, APACHE Ⅱ/Ⅲ: Acute Physiology and Chronic Health Evaluation Ⅱ/Ⅲ.
§The protein intake was replaced by the percentage of protein requirement as it was not available.

Suplementação calórica

Mortalidade

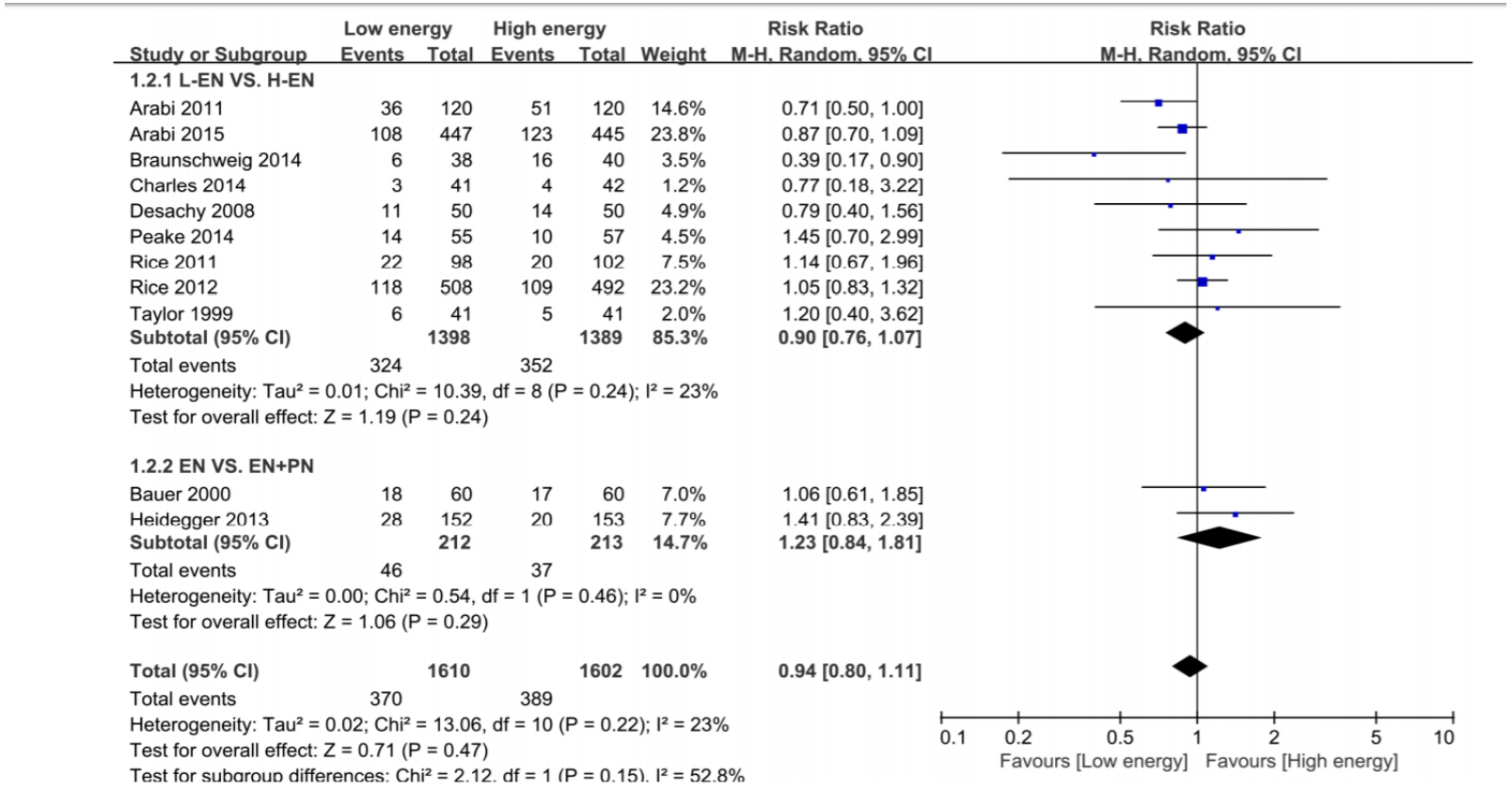


Figure 3. The impact of initial low energy feeding on mortality is shown. MH: Mantel-Haenszel; CI: confidence interval; L-EN: low enteral nutrition; H-EN: high enteral nutrition; EN: enteral nutrition; PN: parenteral nutrition.

Suplementação calórica - conclusão

- Pacientes graves adultos e eutróficos com o TGI funcionante não foram beneficiados pela oferta suplementar de energia. Não se observou diferença na mortalidade e(ou) morbidade infecciosa entre os grupos que receberam oferta baixa (<50% VCT) ou elevada (>80% VCT) de calorias.
- A tolerância a oferta enteral foi melhor no grupo que recebeu baixa oferta.
- A morbidade infecciosa tinha uma tendência a ser menor no grupo com oferta elevada, mas desaparece quando a oferta proteica é ajustada.
- Heterogeneidade dos estudos.
- Desnutridos?

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The online version of this article is located at http://www.minervamedica.it

Minerva Anestesiologica 2016 March;82(3):320-31

REVIEW

Immunonutrients in critically ill patients: an analysis of the most recent literature

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Imunonutrientes – formulações

TABLE I.—*Results of the most recent multicenter studies on immunonutrients in ICU patients.*

	SIGNET Study [20]	REDOX Study [8]	METAPLUS Study [9]
Year of publication	2011	2013	2014
Type of study	RCT	Double blind RCT	RCT
Patients	502 ICU pts	1223 ICU pts (mechanically ventilated, multiple organ dysfunction)	301 ICU pts (mechanically ventilated)
Route	Parenteral	Parenteral + enteral	Enteral
Immunonutrients	Glutamine, selenium	Glutamine, antioxidants	Glutamine, omega-3 FA, antioxidants
Effects of immunonutrients on mortality	No effect	Increased mortality (glutamine)	Increased 6-month mortality in medical ICU pts (P=0.04)
Effects on infection	No effect	Increased urinary tract infections (antioxidants) (P=0.02)	No effect
Effects on LOS	No effect	No effect	No effect

Imunonutrientes – recomendações

TABLE II.—*Recommendations on immunonutrition according to the international guidelines.*

Guidelines	Statement	Strength
2006 ESPEN guidelines [19]	Glutamine should be added to standard enteral formula in burned patients and in trauma patients	Grade A
Id.	There are not sufficient data to support glutamine supplementation in surgical or heterogeneous critically ill patients	
2009 ASPEN guidelines [10]	Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, ω-3 fatty acids, and antioxidants) should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis	Grade A (surgical ICU pts) Grade B (medical ICU pts)
2009 ESPEN guidelines [18]	Fish oil enriched lipid emulsions probably decrease length of stay in critically ill patients	Grade B
2009 CCP Guidelines [12]	We recommend the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)	
2013 CCP Guidelines [13]	When PN is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered. However, we strongly recommend that glutamine NOT be used in critically ill patients with shock and multi-organ failure. There are insufficient data to generate recommendations for IV glutamine in critically ill patients receiving EN	
Id.	The use of an enteral formula with fish oils, borage oils and antioxidants in patients with ALI and ARDS should be considered	
Id.	Based on 4 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients be used for critically ill patients	
2013 SSC Guidelines [11]	We suggest using nutrition with no specific immunomodulating supplementation in patients with severe sepsis	Grade 2C

Imunonutrientes - glutamina

TABLE III.—*Effects of glutamine supplementation on major clinical endpoints in ICU pts: results from the most recent meta-analyses.*

Meta-analysis	Mortality	Infections	ICU days	Hospital days
Bollhalder 2013 [22] 40 RCT 3107 pts (21 on surgical pts 11 on ICU pts)	No (P=0.145)	Reduced (P=0.009)		Reduced (P=0.001)
Wischmeyer 2014 [24] 26 RCT 2482 ICU pts	No (P=0.10)	No (P=0.09)	No (P=0.09)	Reduced (?) (P=0.02) (only in single-centre trials)
Cochrane 2014 [25] 53 studies 4671 pts (both surgical and ICU pts)	No (P=0.10)	Reduced (P=0.00001)	No	Reduced (?) (low quality evidence)
Chen 2014 [26] 18 trials 3383 ICU pts	No (P=0.87)	Reduced (P=0.02)		No (P=0.24)
Maratea 2014 [27] 23 trials 3344 ICU pts	No			

Imunonutrientes – ômega-3

TABLE IV.—*Effects of omega-3 FA supplementation on major clinical endpoints in ICU pts: results from the most recent meta-analyses.*

Meta-analysis	Mortality	Infections	Ventilation days	ICU days	Hospital days
Manzanares 2013 [32] 12 RCT 806 pts	N. (P=0.20)	N. (p=0.35)	N. (P=0.09)	N. (P=0.13)	
Manzanares 2014 [33] 6 RCT 390 pts	No (P=0.08)	No (P=0.35)	No (P=0.17)	No (P=0.84)	
Palmer 2013 [34] 8 studies 391 pts	No (P=0.32)	No (P=0.41)		No (p=0.80)	Reduced (?) (low quality evidence)
Chen 2014 [35] 12 trials 1208 pts	No (P=0.18)				
Zhu 2014 [36] 7 studies 955 pts	No (P=0.44)		No (P=0.36)	No (P=0.33)	
Santacruz 2015 [37] 7 studies 802 ARDS pts	No (p=0.37)		No	Small reduction	

Imunonutrientes - arginina

TABLE V.—*Effects of arginine supplementation on major clinical endpoints in ICU pts: results from the most recent meta-analyses.*

Meta-analysis	Mortality	Infections	ICU days	Hospital days
Marik 2008 [48] 24 studies (3013 pts)	No	No	No	No
CCP Group 2013 [12, 13] 24 studies (2666 pts)	No (P=0.40)	No (P=0.88)	No (P=0.37)	No (P=0.42)

Imunonutrientes - antioxidantes

TABLE VI.—*Effects of antioxidants supplementation on major clinical endpoints in ICU pts: results from the most recent meta-analyses.*

Meta-analysis	Mortality	Infections	Ventilation days	ICU days	Hospital days
Manzanares 2012 [56] 21 studies 2531 pts	Reduced (P=0.002)	No (P=0.08)	Reduced (P=0.02)	No (P=0.38)	No (P=0.73)
Alhazani 2013 [61] 9 studies 792 pts	Reduced (P=0.03)	No (P=0.74)		No (P=0.12)	
Huang 2013 [62] 9 studies 965 pts	Reduced (P=0.04)				
Landucci 2014 [63] 9 studies 921 pts	Reduced (?) (low quality evidence)	No (P=0.67)		No (P=0.09)	

Imunonutrientes - conclusão

1. Glutamina, arginina, ômega-3 e selênio: nutrientes farmacologicamente ativos que poderiam modular a resposta metabólica e inflamatória a cirurgia e (ou) estresse e melhorar a função imune.
2. Esses benefícios foram demonstrados em estudos experimentais e pequenos trabalhos unicêntricos realizados entre 2000 e 2009, mas não foram sustentados por evidências (trabalhos multicêntricos, revisão sistemática e metanálise) recentes, deixando de ser recomendados.
3. Imunonutrientes aumentam o custo e podem causar dano ao paciente grave, particularmente na sepse, não devem ser utilizados rotineiramente.

Probióticos e simbióticos

Manzanares *et al. Critical Care* (2016) 20:262
DOI 10.1186/s13054-016-1434-y

Critical Care

RESEARCH Open Access

Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis

William Manzanares[1], Margot Lemieux[2], Pascal L. Langlois[3] and Paul E. Wischmeyer[4*]

Probióticos e simbióticos

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kecskes 2003	1	22	7	23	0.7%	0.15 [0.02, 1.12]	2003
Lu 2004	8	20	11	20	4.8%	0.73 [0.37, 1.42]	2004
Jain 2004	33	45	26	45	12.8%	1.27 [0.93, 1.72]	2004
McNaught 2005	21	52	22	51	8.3%	0.94 [0.59, 1.48]	2005
Kotzampassi 2006	22	35	27	30	13.7%	0.70 [0.53, 0.93]	2006
Li 2007	8	14	10	11	7.6%	0.63 [0.38, 1.03]	2007
Olah 2007	9	33	15	29	4.9%	0.53 [0.27, 1.02]	2007
Besselink 2008	46	152	41	144	11.1%	1.06 [0.75, 1.51]	2008
Barraud 2010	26	87	29	80	8.9%	0.82 [0.53, 1.27]	2010
Ferrie 2011	14	18	16	18	13.1%	0.88 [0.65, 1.18]	2011
Tan 2011	9	26	15	26	5.4%	0.60 [0.32, 1.12]	2011
Wang 2013	8	62	13	61	3.5%	0.61 [0.27, 1.36]	2013
Lopez de Toro 2014	9	46	13	43	4.1%	0.65 [0.31, 1.36]	2014
Sanaie 2014	2	20	5	20	1.1%	0.40 [0.09, 1.83]	2014
Total (95% CI)		**632**		**601**	**100.0%**	**0.80 [0.68, 0.95]**	
Total events	216		250				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 20.22$, df = 13 (P = 0.09); $I^2 = 36\%$

Test for overall effect: Z = 2.61 (P = 0.009)

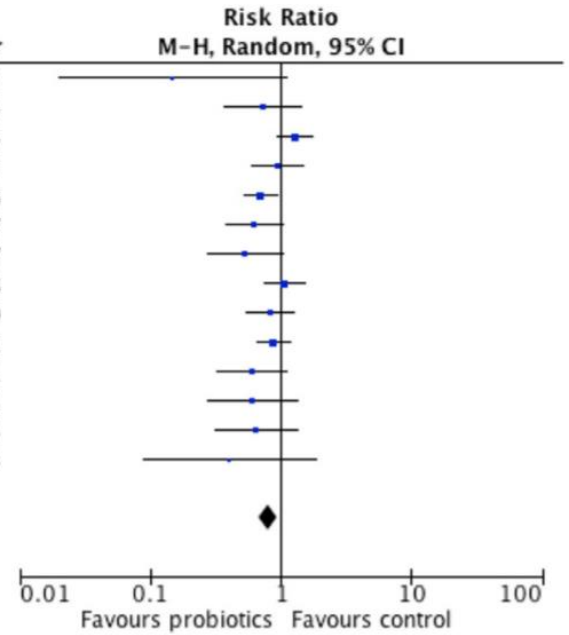


Fig. 1 Effect of probiotics on overall infections (n = 14). *CI* confidence interval, *M-H* Mantel-Haenszel test

Infecções em geral

Probióticos e simbióticos

Pneumonia associada a VM

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kotzampassi 2006	19	35	24	30	20.4%	0.68 [0.48, 0.97]	2006
Klarin 2008	1	23	3	21	0.8%	0.30 [0.03, 2.70]	2008
Forestier 2008	19	102	21	106	10.2%	0.94 [0.54, 1.64]	2008
Knight 2009	12	130	17	129	6.9%	0.70 [0.35, 1.41]	2009
Morrow 2010	13	73	28	73	9.8%	0.46 [0.26, 0.82]	2010
Barraud 2010	23	87	15	80	9.7%	1.41 [0.79, 2.51]	2010
Tan 2011	7	26	13	26	6.2%	0.54 [0.26, 1.13]	2011
Rongrungruang 2015	18	75	22	75	10.9%	0.82 [0.48, 1.40]	2015
Zeng 2016	43	118	59	117	25.1%	0.72 [0.54, 0.97]	2016
Total (95% CI)		**669**		**657**	**100.0%**	**0.74 [0.61, 0.90]**	
Total events	155		202				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.86$, df = 8 (P = 0.27); $I^2 = 19\%$

Test for overall effect: Z = 3.04 (P = 0.002)

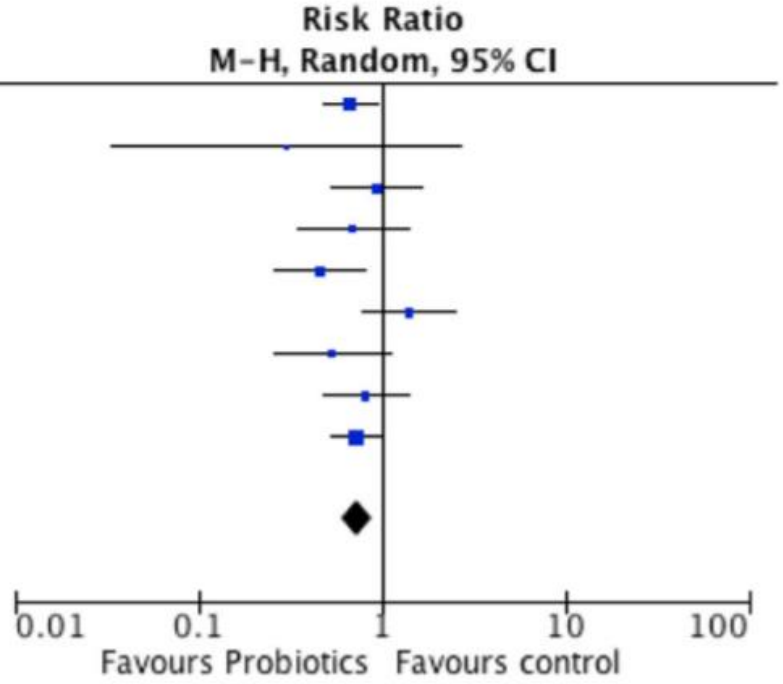


Fig. 2 Effects of probiotics therapy on the incidence of ventilator-associated pneumonia (n = 9). CI confidence interval, *M-H* Mantel-Haenszel test

Probióticos e simbióticos

Mortalidade hospitalar

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tempe 1983	3	20	3	20	1.5%	1.00 [0.23, 4.37]	1983
Kecskes 2003	1	22	2	23	0.6%	0.52 [0.05, 5.36]	2003
Jain 2004	22	45	20	45	16.4%	1.10 [0.71, 1.71]	2004
Lu 2004	2	20	1	20	0.6%	2.00 [0.20, 20.33]	2004
Klarin 2005	2	8	2	7	1.1%	0.88 [0.16, 4.68]	2005
McNaught 2005	18	52	18	51	11.6%	0.98 [0.58, 1.66]	2005
Olah 2007	2	33	6	29	1.4%	0.29 [0.06, 1.34]	2007
Besselink 2008	14	152	9	144	5.0%	1.47 [0.66, 3.30]	2008
Klarin 2008	3	22	2	22	1.1%	1.50 [0.28, 8.12]	2008
Knight 2009	35	130	42	129	22.7%	0.83 [0.57, 1.21]	2009
Frohmader 2010	5	20	3	25	1.9%	2.08 [0.56, 7.68]	2010
Morrow 2010	12	68	15	73	6.9%	0.86 [0.43, 1.70]	2010
Sharma 2011	2	24	2	26	0.9%	1.08 [0.17, 7.10]	2011
Ferrie 2011	2	18	2	18	0.9%	1.00 [0.16, 6.35]	2011
Cui 2013	1	23	1	25	0.4%	1.09 [0.07, 16.39]	2013
Lopez de Toro 2014	19	46	18	43	13.3%	0.99 [0.60, 1.61]	2014
Zeng 2016	26	118	25	117	13.6%	1.03 [0.63, 1.68]	2016
Total (95% CI)		**821**		**817**	**100.0%**	**0.98 [0.82, 1.18]**	
Total events	169		171				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.84$, df = 16 (P = 0.98); $I^2 = 0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

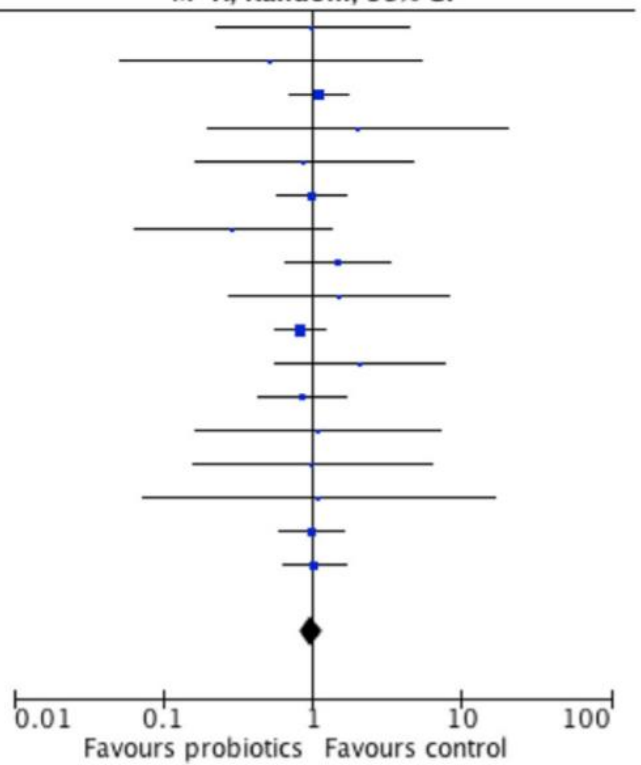


Fig. 3 Effect on hospital mortality (n = 17). *CI* confidence interval, *M-H* Mantel-Haenszel test

Probióticos e simbióticos

Diarréia

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Heimburger 1994	5	16	2	18	1.2%	2.81 [0.63, 12.54]	1994
Bleichner 1997	18	64	24	64	10.5%	0.75 [0.45, 1.24]	1997
Kotzampassi 2006	5	35	10	30	3.0%	0.43 [0.16, 1.12]	2006
Alberda 2007	1	10	2	9	0.6%	0.45 [0.05, 4.16]	2007
Besselink 2008	25	152	28	144	11.1%	0.85 [0.52, 1.38]	2008
Knight 2009	7	130	9	129	3.0%	0.77 [0.30, 2.01]	2009
Morrow 2010	42	68	44	73	33.4%	1.02 [0.79, 1.33]	2010
Barraud 2010	48	87	42	80	29.9%	1.05 [0.79, 1.39]	2010
Rongrungruang 2015	19	75	14	75	7.2%	1.36 [0.74, 2.50]	2015
Total (95% CI)		**637**		**622**	**100.0%**	**0.97 [0.82, 1.15]**	
Total events	170		175				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.44$, df = 8 (P = 0.39); $I^2 = 5\%$

Test for overall effect: Z = 0.34 (P = 0.74)

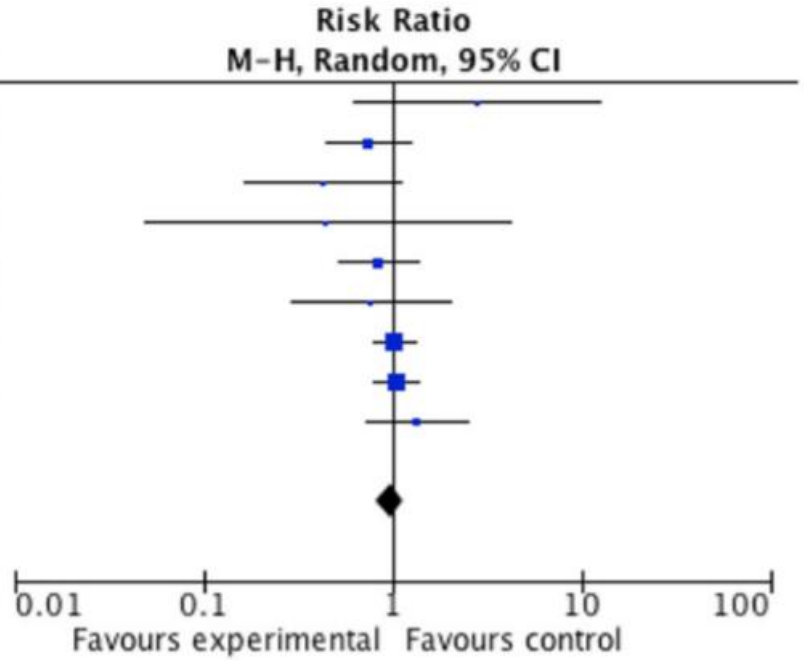


Fig. 4 Effect of probiotics on diarrhea (n = 9). *CI* confidence interval, *M-H* Mantel-Haenszel test

Antibióticos dias de uso

Probióticos e simbióticos

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Frohmader 2010	11.1	4.9	20	9.4	5.8	25	3.7%	1.70 [-1.43, 4.83]
Morrow 2010	13.3	10.4	68	16.3	14.4	70	2.1%	-3.00 [-7.18, 1.18]
Tan 2011	11.9	4.9	26	14.1	6	26	4.1%	-2.20 [-5.18, 0.78]
Zeng 2016	6.8	2	118	7.94	2.9	117	90.0%	-1.14 [-1.78, -0.50]
Total (95% CI)			**232**			**238**	**100.0%**	**-1.12 [-1.72, -0.51]**

Heterogeneity: $Chi^2 = 4.41$, $df = 3$ ($P = 0.22$); $I^2 = 32\%$
Test for overall effect: $Z = 3.62$ ($P = 0.0003$)

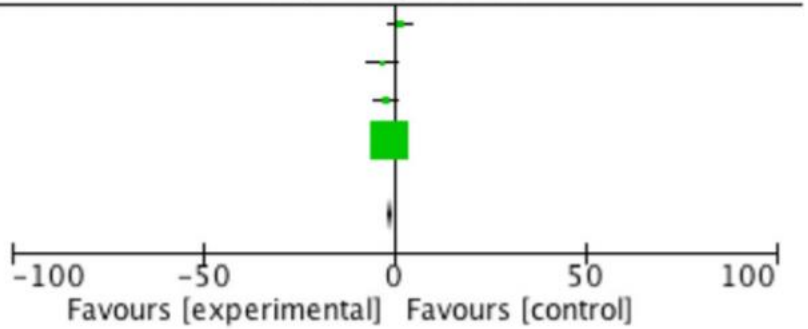


Fig. 5 Effect of probiotics on antibiotic days (n = 4). *CI* confidence interval; *WMD* weighted mean difference

Probióticos e simbióticos - conclusão

- Reduzem complicações infecciosas.
- Podem evitar novos episódios de PAV.
- Grande variabilidade na qualidade dos estudos (30 ao todo, 2972 pacientes).
- *L. plantarum*.

Evidências fortes em nutrição do paciente grave

- Inicio precoce (24 a 48h).
- Via enteral.
- Pacientes eutróficos podem esperar pela via enteral por 7 a 10 dias.

Extrapolação de dados

