3.1 Nutritional Prescription: Use of Indirect Calorimetry vs. Predictive Equations

Question: Does the use of indirect calorimetry vs. a predictive equation for determining energy needs and targeting the nutrition delivery to those needs result in better outcomes critically ill adult patients?

Summary of evidence: There was one level 1 study and eight level two studies reviewed that compared the effectiveness of Indirect Calorimetry (IC) guided nutrition to predictive equations. In six of the studies, enteral nutrition (EN) was supplemented with parenteral nutrition (PN) to make up for the energy deficit in both groups (Singer 2011, Yang 2016, Allingstrup 2017, Gonzalez-Granda 2018, Zhao 2019 and Singer 2020).

Mortality: When the data from all the studies were aggregated, there were no differences in overall mortality between the groups that received IC guided nutrition or predictive equation guided nutrition (RR 0.93, 95% CI 0.66, 1.31, p=0.69, test for heterogeneity I^2 =51%, see Figure 1). Similar results were observed when the data for hospital mortality (RR 0.86, 95% CI 0.59, 1.27, p=0.46, test for heterogeneity I^2 =24%, see Figure 2) and ICU mortality were analysed (RR 0.87, 95% CI 0.69, 1.11, test for heterogeneity I^2 =0%, Figure 3).

Infections: Based on three studies (Singer 2011, Singer 2020, Allingstrup 2017), indirect calorimetry compared to weight-based predictive equation had no effect on total infections (RR 1.29, 95% CI 0.71, 2.36, p=0.40, test for heterogeneity I^2 =78%, Figure 4) or ventilator associated pneumonia (RR 1.33, 95% CI 0.65, 2.75, p=0.44, test for heterogeneity I^2 =62%, Figure 5).

LOS: Indirect calorimetry guided nutrition had no effect on hospital length of stay (WMD 0.49, 95% CI -1.76, 2.74, p=0.67,for heterogeneity I^2 =0%, Figure 6) or ICU length of stay (WMD -0.23, 95% CI -3.84, 3.37, p=0.90, test for heterogeneity I^2 =83%, Figure 7).

Ventilator days: Compared to predictive equations, indirect calorimetry guided nutrition had no effect on duration of mechanical ventilation (WMD -0.31, 95% CI -1.43, 2.06, p=0.72, test for heterogeneity I^2 = 58%, Figure 8).

Nutritional Outcomes: In the Saffle study, diarrhea, hyperglycemia, electrolyte imbalance did not differ between the two groups. Singer et al 2020 reported higher rates of hyperglycemia and use of insulin in the group that received nutrition guided by IC. No differences in number of events of hyperglycemia were seen in Yang 2016 while Allingstrup 2017 reported no significant differences in the highest blood glucose levels in ICU between the two groups. Actual protein intake (grams/day) was significantly higher in the groups receiving EN via IC in all the studies that reported on this outcome (Saffle 1990, Singer 2011, Allingstrup 2017, Gonzalez-Granda 2018, Azevedo 2019 and Singer 2020). A similar increase in energy intakes or % energy goals met was also seen with IC when compared to predictive equations in some studies (Singer 2011, Allingstrup 2017, Gonzalez-Granda 2018 and Singer 2020) while was not observed in others (Saffle 1990, Landes 2016) and or was not reported (Yang 2016, Zhao 2019).

Conclusions:

1) The use of IC compared to predictive equations to meet nutrition needs has no effect on mortality.
3) The use of IC compared to predictive equations as a guide to nutritional delivery has no effect on infections or ventilator associated pneumonia.
4) The use of IC compared to predictive equations as a guide to nutritional delivery has no effect on hospital, ICU length of stay, or duration of ventilation.
5) The use of IC compared to predictive equations may be associated with improved nutritional intake.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating indirect calorimetry vs. predictive equation in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)	
				Indirect Calorimetry	Predictive Equation	Indirect Calorimetry	Predictive Equation
1) Saffle 1990*	Burns 47 % TSBA N=49	C.Random: not sure ITT: yes Blinding: no (7)	EN via Indirect calorimetry with measurements X 3/week vs. Curreri formula. Within each arm, patents were further divided to receive 1 Kcal/mL lower protein formula (Osmolite HN) vs. 1 Kcal/mL higher protein formula (Isotene HN) Isocaloric, non isonitrogenous	3/26 (12)	2/23 (9)	NR	NR
2) Singer 2011	Mechanically ventilated critically ill patients (Mixed medical, surgical, trauma) N=130	C.Random: Yes ITT: No Blinding: No (8)	EN via indirect calorimetry with measurements Q48H supplemented with PN and energy delivery adjusted accordingly vs. EN (using 25kcal/kg/day and not readjusted for 14 days). PN attempted to make up shortfall Non isocaloric, non-isonitrogenous	**ICU** 16/56 (29) **Hospital** 16/56(29) **60-day** 24/56 (58)	**ICU** 17/56 (30) **Hospital** 27/56 (48) **60-day** 29/56 (48)	**Total** 37/56 (66) **VAP** 18/56 (32)	**Total** 20/56 (36) **VAP** 9/56 (16)
3) Landes 2016	Mechanical ventilated patients N=27	C.Random: Yes ITT: Yes Blinding: Yes (9)	EN via indirect calorimetry with measurements at study start and every week X 3 weeks vs. EN (Harris Benedict equation or 25 Kcal/kg/day) Isocaloric. Isonitrogenous: ?	NR	NR	NR	NR
4) Yang 2016	Mechanical ventilated hemodynamically	C.Random: no ITT: yes Blinding: no	EN via indirect calorimetry with measurements at day 0, 3, 7 and 14 vs. EN	**28 day** 1/30 (3.3)	**28 day** 7/30 (23.3); p=0.02	NR	NR

	stable patients with sepsis N=60	(7)	(Harris Benedict equation). PN used if needed. Isocaloric, isontrogenous:?				
5) Allingstrup 2017	Mixed ICU patients. Single centre. N=203	C.Random: yes ITT: no Blinding: single (8)	EN via indirect calorimetry with protein dosed at 1.5 g/kg/d, 100% of nutrition prescription given on first full study day vs. feeds dosed at 25 kcal/kg, EN started within 24h and gradually increased. PN as needed. Non-isocaloric, non-isonitrogenous	**Day 28** 20/100 (20) **Day 90** 30/100 (30) **6 Months** 37/100 (37)	**Day 28** 21/99 (21); p=0.83 **Day 90** 32/99 (32); p=0.72 **6 Months** 34/99 (34); p=0.70	**Any nosocomial infection** 19/100 (19)	**Any nosocomial infection** 12/99 (12); p=0.18
6) Gonzalez-Granda 2018	Mechanical ventilated patients N=76	C.Random: Not sure ITT: no Blinding:no (6)	EN via indirect calorimetry with measurements within 24-72 hrs after intubation and weekly for 3 weeks vs. EN (25 Kcal/kg/day). PN used to supplement calories. Non-isocaloric, non-isonitrogenous.	**ICU** 3/20 (15) **Hospital** 5/20 (25)	**ICU** 3/20 (15) **Hospital** 3/20(15)	NR	NR
7) Azevedo 2019	Mechanical ventilated patients expected to stay in ICU ≥2 days N=138	C.Random: no ITT: no Blinding:no (5)	EN via indirect calorimetry with measurements daily for first 3 days, then every 2 days until day 10) and protein 2.0-2.2g/kg vs. EN based on 25 kcal/kg/day & protein 1.4-1.5 g/kg/day Isocaloric, non-isontrogenous.	**ICU** 22/57 (38.5) **Hospital** 26/57 (45.6)	**ICU** 28/63 (44.4); p=0.69 **Hospital** 29/63 (46); p=0.88	NR	NR
8) Zhao 2019	Mechanical ventilated patients expected to receive EN/PN for >7days N=76	C.Random: No ITT: no Blinding:no (6)	EN via indirect calorimetry with measurements from day 1-7 vs. EN via Harris Benedict equation Day 1-7. PN used if needed. Isocaloric, isontrogenous:?	**28 day** 5/29 (17.2)	**28 day** 7/29 (24.1); p=0.52	NR	NR

9) Singer 2020**	Ventilated critically ill patients N=417 Multicenter N=7	C.Random: Yes ITT: Yes Blinding: No (9)	EN (80-100% energy needs) via indirect calorimetry with measurements vs. EN (using 20-25kcal/kg/day). PN was used to make up shortfall in EN energy from day 3 onwards. Non isocaloric, non-isonitrogenous	**ICU** 45/209 (21.5) **3 month** 67/209 (32.1) **180 day** 79/209 (37.8)	**ICU** 53/208 (25.5) **3 month** 75/208 (36.1) **180 day** 78/208 (37.5)	31/209 (14.8) **VAP** 22/209 (10.5)	40/208 (19.2) **VAP** 23/208 (11.1)

Table 1. Randomized studies evaluating indirect calorimetry vs. predictive equation in critically ill patients (continued)

Study	**LOS days**		**Ventilator days**		**Other**	
	Indirect Calorimetry	**Predictive Equation**	**Indirect Calorimetry**	**Predictive Equation**	**Indirect Calorimetry**	**Predictive Equation**
1) Saffle 1990*	**Hospital** 48.8 ± 4.5 (26)	**Hospital** 48.5 ± 5.2 (23)	NR	NR	**Diarrhea** 34.6 % **Hyperglycemia** 38.5 % **Nausea** 26.9 % **Electrolyte imbalance** 30.8 % **Actual calories intake (kcals/day)** 3530 ± 134 **Actual protein intake (g/day)** 153 ± 7.1	 34.8 % 43.5 % 34.8 % 39.1 % 3490 ± 132 116 ± 6.7; p<0.01
2) Singer 2011	**ICU** 17.2 ± 14.6 (56) **Hospital** 33.8 ± 22.9 (56)	**ICU** 11.7 ± 8.4 (56) **Hospital** 31.8 ± 27.3 (56)	16.1 ± 14.7 (56)	10.5 ± 8.3 (56)	**Energy (kcal/day)** 2086 ± 460 **Protein (g/day)** 76 ± 16	 1480 ± 356 53 ± 16

3) Landes 2016	NR	NR	48.6±21.7 (15)	46.0±31.2 (12)	**Energy intake (Kcal/day)** 1976.2±481.1 2067.33±340.8 **% Energy received** 86.5±12.4% 77±17.6%
4) Yang 2016	**ICU** 8.06 (7.18-12.07)	**ICU** 10.31 (8.11-16.38); p=0.039	6.67 (4.68-9.48)	6.56 (3.88-9.72); p=0.774	**Prescribed energy intake Kcal, day 0** 1892 (1697-2206) vs. 1540 (1436-1731), **Prescribed energy intake Kcal, day 3** 1938 (1753-2259) vs. 1487 (1349-1724), **Prescribed energy intake Kcal, day 7** 1927 (1740-2287) vs. 1487 (1290-1647), **Prescribed energy intake Kcal, day 14** 1879 (1636-2397) vs. 1461 (1215-1575) **# events of bilirubin ≥2 times normal** 36/95 (37.9) vs.27/93 (31.1); p=0.20 **# events of hyperglycemia** 11/95 (11.6) vs. 8/93 (8.6); p=0.78 **# events of hypoglycemia** 3/95 (3.2) vs. 3/93 (3.2); p=0.78
5) Allingstrup 2017	**ICU, 6 month survivors** 7 (5-22) **Hospital, 6 month survivors** 30 (12-53)	**ICU, 6 month survivors** 7 (4-11); p=0.21 **Hospital, 6 month survivors** 34 (14-53); p=1.0	NR	NR	**% of energy goals met** 97 (91-100) vs. 64 (40-84), p<0.001 **% of protein goals met** 97 (75-115) vs. 45 (27-62); p<0.001 **Protein intake g/kg/d** 1.47 (1.13-1.69) vs. 0.5 (0.29-0.69) **Highest blood glucose in ICU, mmol/L** 11.0 (9.3-12.4) vs. 9.4 (8.5-10.9)
6) Gonzalez-Granda 2018	**ICU** 13 ± 8 (20) **Hospital** 31 ± 24 (20)	**ICU** 24 ± 20 (20) **Hospital** 40 ± 23 (20)	9 ± 8 (20)	10 ± 5 (20)	**Energy Intake (Kcal/kg/day)** 20.4 ± 5.7 20.0 ± 7.5 **% energy intake** 98%± 8% 79% ±29% p<0.05 **Protein intake (g/kg/d)** 78±18 59±2 p<0.01 **% protein intake** 91±24 73±33 p=0.12

7) Azevedo 2019	**ICU** 21 (13-33) 18	**ICU** 18 (10-35); p=0.56	9 (5-14)	9 (5-14); p=0.64	**Energy requirement, kcal/day** 1554 (1383-1862) vs. 1450 (1300-1625); p=0.02 **Protein requirement, g/kg/day** 2.1 (2.1-2.1) vs. 1.45 (1.45-1.45) ; p<0.0001 **Energy received, kcal/day** 1139 (890-1278) vs. 1140 (889-1331); p=0.70 **Protein received, g/kg/day** 1.69 (1.33-1.80) vs. 1.13 (0.97-1.34); p<0.0001 **Handgrip strength at ICU discharge** **Males** 18 (15-25) (n=15) vs. 23.5 (13.7-32.0) (n=14); p=0.35 **Females** 8 (2-17) (n=9) vs. 14 (7-22.5) (n=13); p=0.18
8) Zhao 2019	**ICU** 8.45 ± 2.44 (29)	**ICU** 10.41 ± 3.11 (29); p=0.009	3.89 ±1.14 (29)	4.71 ± 1.08 (29); p=0.007	**Prescribed energy intake Kcal/day** **Day 1-7, mean SD** 1567.34±143.39 vs. 1615.49± 159.69
9) Singer 2020	**ICU** 13.1± 12.5 (199) **Hospital** 26.8 ± 28.9 (199)	**ICU** 12.2 ± 8.9 (207) **Hospital** 25 2 ± 16 (207)	10.2 ± 9.3 (199)	9.8 ± 8.0 (207)	**Mean Energy delivered (kcal/day**) 1746±755 1301±535 p=0.04 **Mean daily energy balance (kcal)** -282±896 - 885±535 p<0.001 **Mean Protein delivered (g/day** 77.3±53.0 62.4±33.9 p =0.03 **Daily highest blood glucose (mg/dL**) 187±59 148±68, p=0.16 **Administered insulin (iu)** 72±43 48±49, p=0.06

* Saffle 1990: for this section, the data shown is the combined high protein and low protein IC vs. high protein and low protein Curreri groups
** Singer 2020: mortality, infection and VAP data may differ from publication but confirmed by author

C.Random: concealed randomization
† presumed hospital mortality unless otherwise specified
ITT: intent to treat
NR: not reported

( ): mean ± standard deviation (number)
VAP: ventilator associated pneumonia
ICU: intensive care unit
LOS: length of stay

Figure 1. Overall Mortality

	Indirect calorimetry		Predictive equations			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Saffle	3	26	2	23	3.6%	1.33 [0.24, 7.26]	1990
Singer 2011	16	56	27	56	18.5%	0.59 [0.36, 0.97]	2011
Yang	1	30	7	30	2.6%	0.14 [0.02, 1.09]	2016
Allingstrup	20	100	21	199	16.6%	1.90 [1.08, 3.33]	2017
Gonzales-Granda	5	20	3	20	5.7%	1.67 [0.46, 6.06]	2018
Zhao	5	29	7	29	8.2%	0.71 [0.26, 1.99]	2019
Azevedo	26	57	29	63	21.7%	0.99 [0.67, 1.46]	2019
Singer 2020	45	209	53	208	23.0%	0.84 [0.60, 1.20]	2020
Total (95% CI)		**527**		**628**	**100.0%**	**0.93 [0.66, 1.31]**	
Total events	121		149				

Heterogeneity: Tau² = 0.10; Chi² = 14.18, df = 7 (P = 0.05); I² = 51%
Test for overall effect: Z = 0.40 (P = 0.69)

Risk Ratio
M-H, Random, 95% CI

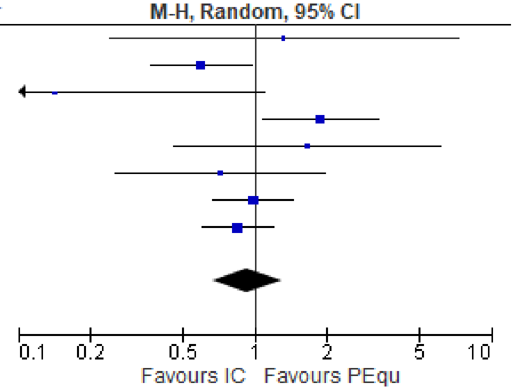


Figure 2. Hospital Mortality

	Indirect calorimetry		Predictive equations			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Saffle	3	26	2	23	4.9%	1.33 [0.24, 7.26]	1990
Singer 2011	16	56	27	56	37.6%	0.59 [0.36, 0.97]	2011
Gonzales-Granda	5	20	3	20	8.1%	1.67 [0.46, 6.06]	2018
Azevedo	26	57	29	63	49.4%	0.99 [0.67, 1.46]	2019
Total (95% CI)		**159**		**162**	**100.0%**	**0.86 [0.59, 1.27]**	
Total events	50		61				

Heterogeneity: Tau² = 0.04; Chi² = 3.94, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.74 (P = 0.46)

Risk Ratio
M-H, Random, 95% CI

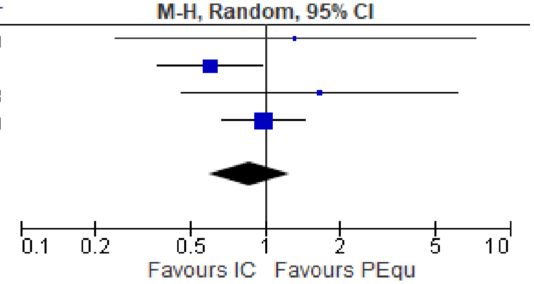


Figure 3. ICU Mortality

Study or Subgroup	Indirect calorimetry Events	Indirect calorimetry Total	Predictive equations Events	Predictive equations Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Singer 2011	16	56	17	56	17.7%	0.94 [0.53, 1.67]	2011
Gonzales-Granda	3	20	3	20	2.7%	1.00 [0.23, 4.37]	2018
Azevedo	22	57	28	63	31.7%	0.87 [0.57, 1.33]	2019
Singer 2020	45	209	53	208	48.0%	0.84 [0.60, 1.20]	2020
Total (95% CI)		**342**		**347**	**100.0%**	**0.87 [0.69, 1.11]**	
Total events	86		101				

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)

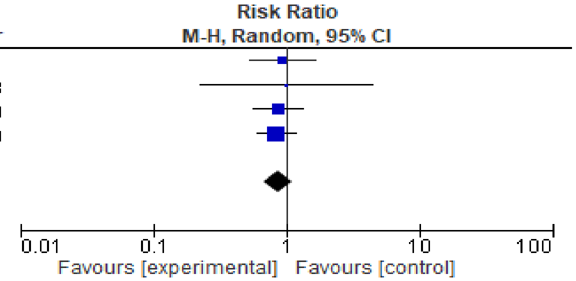


Figure 4. Total Infections

Study or Subgroup	Indirect calorimetry Events	Indirect calorimetry Total	Predictive equations Events	Predictive equations Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Singer 2011	37	56	20	56	36.3%	1.85 [1.24, 2.76]	2011
Allingstrup	19	100	12	99	28.2%	1.57 [0.80, 3.05]	2017
Singer 2020	31	209	40	208	35.5%	0.77 [0.50, 1.18]	2020
Total (95% CI)		**365**		**363**	**100.0%**	**1.29 [0.71, 2.36]**	
Total events	87		72				

Heterogeneity: Tau² = 0.22; Chi² = 9.23, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 0.84 (P = 0.40)

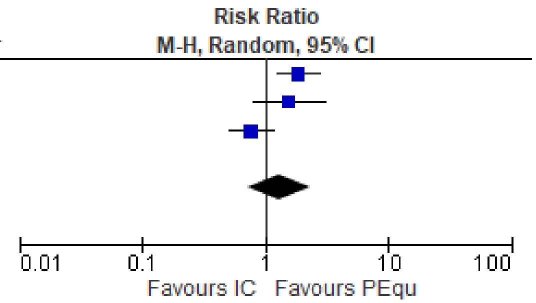


Figure 5. Ventilator Associated Pneumonia

Study or Subgroup	Indirect calorimetry Events	Indirect calorimetry Total	Predictive equations Events	Predictive equations Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Singer 2011	18	56	9	56	45.3%	2.00 [0.98, 4.06]	2011
Singer 2020	22	209	23	208	54.7%	0.95 [0.55, 1.65]	2020
Total (95% CI)		**265**		**264**	**100.0%**	**1.33 [0.65, 2.75]**	
Total events	40		32				

Heterogeneity: Tau² = 0.17; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.78 (P = 0.44)

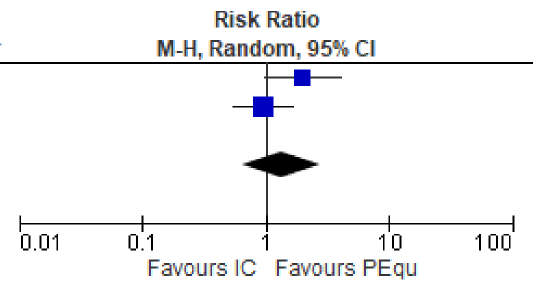


Figure 6. Hospital Length of stay

	Indirect calorimetry			Predictive equations				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Saffle	48.8	4.5	26	48.5	5.2	23	67.5%	0.30 [-2.44, 3.04]	1990
Singer 2011	33.8	22.9	56	31.8	27.3	56	5.8%	2.00 [-7.33, 11.33]	2011
Gonzales-Granda	31	24	20	40	23	20	2.4%	-9.00 [-23.57, 5.57]	2018
Singer 2020	26.8	28.9	199	25.2	16	207	24.3%	1.60 [-2.97, 6.17]	2020
Total (95% CI)			**301**			**306**	**100.0%**	**0.49 [-1.76, 2.74]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.98$, df = 3 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 0.43 (P = 0.67)

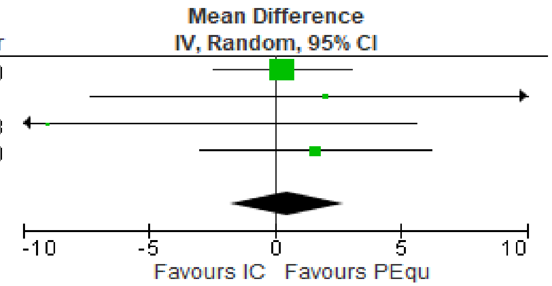


Figure 7. ICU Length of Stay

	Indirect calorimetry			Predictive equations				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Gonzales-Granda	13	8	20	24	20	20	10.4%	-11.00 [-20.44, -1.56]
Singer 2011	17.2	14.6	56	11.7	8.4	56	23.4%	5.50 [1.09, 9.91]
Singer 2020	13.1	12.5	199	12.2	8.9	207	32.1%	0.90 [-1.22, 3.02]
Zhao	8.45	2.44	29	10.41	3.11	29	34.1%	-1.96 [-3.40, -0.52]
Total (95% CI)			**304**			**312**	**100.0%**	**-0.23 [-3.84, 3.37]**

Heterogeneity: $Tau^2 = 9.37$; $Chi^2 = 17.29$, df = 3 (P = 0.0006); $I^2 = 83\%$
Test for overall effect: Z = 0.13 (P = 0.90)

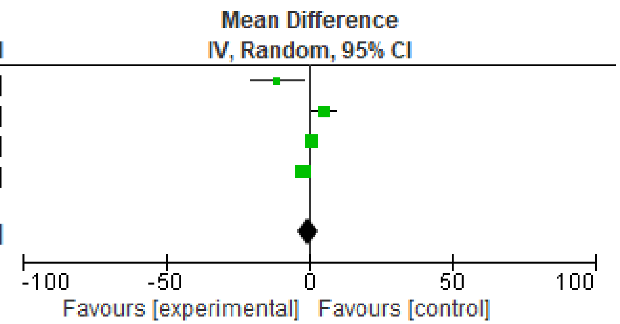
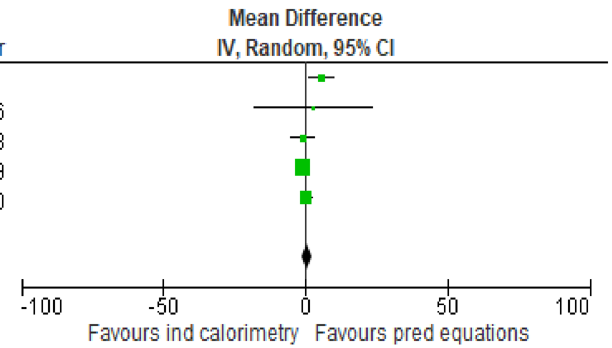


Figure 8. Duration of Mechanical Ventilation

	Indirect calorimetry			Predictive equations				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Singer 2011	16.1	14.7	56	10.5	8.3	56	11.6%	5.60 [1.18, 10.02]	2011
Landes	48.6	21.7	15	46	31.2	12	0.7%	2.60 [-18.19, 23.39]	2016
Gonzales-Granda	9	8	20	10	5	20	12.8%	-1.00 [-5.13, 3.13]	2018
Zhao	3.89	1.14	29	4.71	1.08	29	43.1%	-0.82 [-1.39, -0.25]	2019
Singer 2020	10.2	9.3	199	9.8	8	207	31.8%	0.40 [-1.29, 2.09]	2020
Total (95% CI)			**319**			**324**	**100.0%**	**0.31 [-1.43, 2.06]**	

Heterogeneity: $Tau^2 = 1.76$; $Chi^2 = 9.59$, $df = 4$ ($P = 0.05$); $I^2 = 58\%$
Test for overall effect: $Z = 0.35$ ($P = 0.72$)



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Excluded Studies	Reasons
Brandi LS, Bertolini R, Calafa M. Indirect calorimetry in critically ill patients: Clinical applications and practical advice. Nutrition 1997;13(4):349-358	Not RCT
Nataloni S, Gentili N, Marini B, Guidi A et al. Nutritional assessment in head injured patients through the study of rapid turnover visceral proteins. Clin Nutr 1999;18(4):247-51	No clinical outcomes
Mentec H, Dupont H, Bocchetti M et al. Upper digestive intolerance during enteral nutrition in critically ill patients: Frequency, risk factors, and complications. Crit Care Med 2001;29(10):1955-1961	Not RCT
Cheng CH, Chen CH, Wong Y et al. Measured versus estimated energy expenditure in mechanically ventilated critically ill patients. Clin Nutr 2002;21(2):165-72	Not RCT
Lo HC, Lin CH, Tsai LJ. Effects of hypercaloric feeding on nutrition status and carbon dioxide production in patients with long-term mechanical ventilation. JPEN J Parentr Enteral Nutr 2005;29(5):380-397	Patients in chronic respiratory care unit; no clinical outcomes

Shi J, Xi L, Chi T, Song J, Wang Z. Application value of resting energy monitoring in nutritional support therapy for mechanical ventilation patients. Zhonghua wei zhong bing ji jiu yi xue. 2019;31(1):98–101	No clinical outcomes