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Enteral and parenteral nutrition in cancer patients, a comparison of complication rates: an updated systematic review and (cumulative) metaanalysis

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ABSTRACT

Introduction

Weight loss in cancer patients is a worrisome constitutional change predicting disease progression and shortened survival time. A logical approach to counter some of the weight loss is to provide nutritional support, administered through enteral nutrition (EN) or parenteral nutrition (PN). The aim of this paper was to update the original systematic review and meta-analysis previously published by Chow *et al*, while also assessing publication quality and effect of RCTs on the metaconclusion over time.

Methods

A literature search was carried out; screening was conducted for randomized controlled trials published in January 2015 up until December 2018. The primary endpoints were the percentage of patients achieving no infection and no nutrition support complications. Secondary endpoints included proportion of patients achieving no major complications and no mortality. Review Manager (RevMan 5.3) by Cochrane IMS and Comprehensive Meta-Analysis (Version 3) by Biostat were used for meta-analyses of endpoints and assessment of publication quality.

Results

An additional 7 studies were identified since our prior publication, leading to 43 papers included in our review. The results echo those previously published; EN and PN are equivalent in all endpoints except for infection. Subgroup analyses of studies only containing adults indicate identical risks across all endpoints. Cumulative meta-analysis suggests that meta-conclusions have remained the same since the beginning of publication time for all endpoints except for the endpoint of infection, which changed from not favouring to favouring EN after studies published in 1997. There was low risk of bias, as determined by assessment tool and visual inspection of funnel plots.

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Conclusions

The results support the current European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines recommending enteral over parenteral nutrition, when oral nutrition is inadequate, in adult patients. Further studies comparing EN and PN for these critical endpoints appear unnecessary, given the lack of change in meta-conclusion and low publication bias over the past decades.

Keywords: parenteral nutrition (PN), enteral nutrition (EN), cancer patients, malnutrition, tube feeding (TF), standard care (SC)

INTRODUCTION

Unintentional weight loss for cancer patients is a worrisome constitutional change predicting disease progression and shortened survival time [1-2]. A logical approach to counter weight loss is to provide nutritional support, administered through enteral nutrition (EN) or parenteral nutrition (PN) [3-4]. Historically, these approaches are accompanied with concerns of increased complications and costs; EN may hence be the preferred modality, due to its lower costs, fewer complications, and perceived better outcomes [4-6]. Over the past several decades, however, there have been substantial changes in clinical nutrition – the cost effectiveness of nutrition support has significantly increased through adoption of "all-in-one bags" for parenteral nutrition, novel enteral and parenteral formulas, peripheral insertion, and new materials for venous and enteral accesses, just to name a few [7]. New strategies, including standardized "bundles" of evidence-based interventions and strict policies of antisepsis, have also been developed and implemented to reduce the risk of complications [7].

The first meta-analysis comparing complication rates of EN and PN in cancer patients was published in 2016 [7], and looked at endpoints of infection, nutrition support complications, major complications and mortality. It included 36 articles [8-43], and reported that similar rates of nutrition support complications, major complications and mortality were observed between patients receiving EN and PN. Infection rates were reported to be slightly higher among PN patients.

Since the original review, more trials have been published and additional information has the potential for a more comprehensive meta-analysis with greater confidence in the principle conclusions. Moreover, the original review did not assess publication quality, or quantitatively assess for publication bias. With over 1,000 patients randomized to EN and PN each, the current

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meta-analysis may be sufficiently powered to offer a precise point estimate and recommend trial resources be dedicated elsewhere. To determine the effect of the latest randomized controlled trials (RCTs), a cumulative meta-analysis may adequately assess the meta-conclusion over time, as RCTs with new data are published.

The aim of this paper was to compare complication rates for EN and PN cancer patients, through updating the systematic review and meta-analysis previously published, while also assessing publication quality and effect of RCTs on the meta-conclusion over time.

METHODS

Search Strategy

A literature search was carried out in Ovid MEDLINE, Embase Classic and Embase, and Cochrane Central Register of Controlled Trials. The search included studies up until the last week of December 2018 and was limited to English-language studies and RCTs. Search terms included "PN", "EN" and "comparative studies" [Appendix 1], similar to the prior review by Chow *et al* [7]. Reference lists of included studies were also included in the search.

Selection Criteria

Screening was conducted by two authors (RC, LC); where disagreement occurred, discussion and consensus was achieved with input from a third author (NC); Cohen's kappa coefficient documented the inter-rater agreement. Titles and abstracts published after January 2015 and beyond were screened and deemed relevant for full-text review if there was mention of parenteral nutrition and enteral nutrition, and additionally stated that the two nutrition support treatments

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were compared. Following full-text review, studies were included if over 50% of the study population had any form and any stage of cancer, in line with the prior review by Chow *et al* [7].

Endpoints

The primary endpoints were the percentage of patients achieving no infection and no nutrition support complications. Secondary endpoints included proportion of patients achieving no major complications and no mortality.

The definition of endpoints is the same as those reported by the former review published by Chow *et al.* [7]. Minor infections were recorded as reported in studies; when studies provided a breakdown of infection complications, the endpoint "minor infections" was the summation of wound infection, pneumonia and sepsis. Nutrition support complications were recorded as published in studies, or reported as the summation of nausea, vomiting and diarrhea events. Major complication events included major complications and morbidity are reported, as disclosed in studies. Mortality rate was noted as they were recorded in literature.

Additional study characteristics recorded include type of EN (standard care (SC) and tube feeding (TF)), nutrition status of population (including individuals who are malnourished or deemed with protein-energy malnutrition (PEM); studies not mentioning PEM were assumed to have no malnourished patients as we postulated that this demographic would be reported if PEM patients were prevalent) and age of population (children as defined by study, typically 21 years and younger, or adults).

Statistical Analysis

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The Mantel-Haenszel model was applied and a random effects analysis model was used to generate risk ratios (RR) and their accompanying 95% confidence intervals (CIs). A *p*-value of less than 0.05 was deemed statistically significant in the test for overall effect; a heterogeneity test with *p*-value greater than 0.05 was considered suitable. For all endpoints, we used the number of patients that did not experience the outcomes as the event numbers, to enable calculation of risks and risk ratios. Test for heterogeneity was conducted to determine whether the size of the effect was equal in all included studies. Review Manager (RevMan 5.3) by Cochrane IMS was used for the aforementioned analyses, to update the previously published analyses and forest plots. Comprehensive Meta-Analysis (Version 3) by Biostat was also used to conduct a cumulative meta-analysis, and assess the effect of studies to the meta-conclusion over publication time.

Assessment of Publication Quality

Funnel plots were generated by Review Manager (RevMan 5.3) to visually assess for publication bias. The Cochrane Risk of Bias assessment tool was employed to assess study quality of the included RCTs.

RESULTS

A total of 216 titles and abstracts were screened, of which 60 were identified for full-text screening (Cohen's kappa = 0.9239). The updated search yielded 7 additional studies [44-50] for inclusion in this systematic review and meta-analysis (Cohen's kappa = 0.7931) [Appendix 2]. The studies all reported on TF and studied adults. The study by Harvey *et al.* [46] included patients classified as PEM.

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Infection

PN was slightly statistically superior with respect to infection (RR = 1.11; 95% CI: 1.04-1.19). Subgroup analyses by EN indicated that TF is superior to PN, whereas SC is equivalent. In patients suffering from PEM, PN and EN are equivalent. A higher risk of infection was noted among adult studies; no greater risk was reported among studies in children [Figure 1]. The aforementioned meta-conclusion, favouring PN, has remained unchanged since 1997; the cumulative RR remains in favour of PN with the inclusion of each published study dating to 1997 [Figure 2].

Nutrition Support Complications

Risk of nutrition support complications in EN and PN patients were equivalent (RR = 1.00; 95% CI: 0.96-1.05). Subgroup analyses by modality of EN, nutrition status and age of population reveal that the rate of complications is equivalent within subgroups too [Figure 3]. Since the first study, the meta-conclusion has not favoured EN or PN [Figure 4].

Major Complications

Neither EN nor PN were superior with respect to lower incidence of major complications. No studies on children reported on this endpoint. Subgroup analyses of TF, SC, PEM studies and non-PEM studies reported a similar conclusion [Figure 5]. The meta-conclusion has remained the same since the first publications [Figure 6].

Mortality

Analyses and subgroup analyses indicate equivalent mortality rates between EN and PN [Figure 7]. The meta-conclusion over time has remained the same [Figure 8].

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Heterogeneity

Unsuitable levels of heterogeneity were observed for all analyses of the endpoint "No infection", except for subgroup analyses of studies reporting on children [Figure 1]. Subgroup analyses of "No nutrition support complications" of subgroup SC, non-PEM studies, and child studies had appropriate levels of heterogeneity; other analyses of this endpoint have unsuitable levels [Figure 3]. These unsatisfactory levels may be a consequence of different clinical methodologies, such as different definitions of endpoints across different studies. All analyses of "No major complications" except for subgroup analyses of SC had satisfactory heterogeneity [Figure 5]. Satisfactory levels were observed for all analyses of endpoint "No mortality" [Figure 7].

Publication Quality

The majority of studies had low risk of bias [Appendix 3]. No obvious publication biases exist, as noted by lack of glaring asymmetries upon visual inspection of funnel plots [Appendices 4-7].

DISCUSSION

This systematic review and meta-analysis comparing complication rates between cancer patients administered EN or PN includes 43 studies, which is the highest-powered analysis to date in the cancer setting: the original meta-analysis by Chow *et al.* in 2016 comprised of 36 studies, while Braunschweig *et al.*'s study in 2001 had only 7 studies in their subgroup analyses of cancer patients [51]. The results in this study echo those published in 2016; EN and PN are equivalent in all endpoints except for infection [7]. In fact, cumulative meta-analysis suggests that meta-conclusions have remained the same since the beginning of publication time (i.e. the first published

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RCT) for all endpoints except for the endpoint of infection, which changed from not favouring to favouring EN after studies published in 1997.

Compared to the original review, this review involved additional analyses. The prior review conducted subgroup analyses only by type of EN and nutrition status; this review also investigated endpoints by age of the study population. For studies containing children, PN was equivalent to EN in all three endpoints – infection, nutrition support complications, and mortality; no studies reported on major complications/morbidity. In adults, the conclusion remains unchanged: EN is superior to PN only in infection. These results hence support the current European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines that suggests enteral over parenteral where the gastrointestinal tract works, when oral nutrition is inadequate [52].

Lack of bias, as assessed by the Cochrane Risk of Bias assessment tool and through visual inspection of funnel plots, suggests that the existing literature appropriately documents critical endpoints of PN compared to EN; RCTs, in line with the nature of their study type, did not have critical methodology flaws/biases. This, when considered in conjunction with the results of the cumulative meta-analyses examining studies over the past two decades has only refined our point estimate and has not altered our meta-conclusion, suggests that no new trials are required in this setting to look into these critical endpoints. When considering whether a cancer patient should be administered EN or PN, other considerations should be pondered.

PN has been reported to require less time in improving a patient's nutritional state, which can minimize hospital stays and help expedite turnover of hospital beds to care for more patients [43]. However, EN is nearly half the cost of PN, and may be more fiscally favourable [20]. PN has also been reported to be more beneficial for cancer surgery patients; PN may continue uninterrupted during settings where oral feeding may need to be withheld, such as during some

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preoperative diagnostic procedures [13]. However, the results of this meta-analysis suggest that risk of major complications/morbidity and mortality of both nutrition support routes are still equivalent.

This review has its limitations. The reporting of endpoints across studies was not standardized: different definitions and recording methods for infections, nutrition support complications, and major complication outcomes existed. To accurately capture and extract endpoints, we reviewed and contacted corresponding authors when necessary for clarification of endpoints and collection of more data. Overall risk ratios computed by cumulative meta-analyses and standard meta-analysis forest plots differed slightly, due to rounding. Assessment of publication bias via funnel plots did not include accompanying quantitative metrics such as Egger's test; the lack of asymmetry, however, clearly indicates no publication bias.

This systematic review reaffirms the conclusions originally reported by the meta-analysis by Chow *et al*: that neither PN nor EN are superior for all endpoints (major complications, mortality, nutrition support complications) other than infection. Cumulative meta-analyses, in fact, indicate that the meta-conclusion has not changed for several decades; new trials investigating these endpoints are likely unnecessary as they would add little value to the existing body of literature. Subgroup analyses of studies only containing adult patients show no superiority of PN compared to EN, supporting ESPEN's latest guidelines recommending EN should be provided for cancer patients where oral intake is inadequate or they are already malnourished, given that their gastrointestinal tract is functional.

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Figure 1.1

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.1.1 Tube Feeding								
Lim et al 1981	7	12	7	12	0.9%	1.00 [0.51, 1.97]	1981	
Sako et al 1981	30	33	34	36	4.8%	0.96 [0.84, 1.10]	1981	
Hamaoui et al 1990	10	11	8	8	3.1%	0.93 10.71, 1.211	1990	<u> </u>
Von Mevenfeldt et al 1992	20	50	8	51	0.8%	2.55 [1.24, 5.25]	1992	
lovinelli et al 1993	19	24	20	24	3.1%	0.95 [0.72, 1.25]	1993	
Sand et al 1997	10	13	11	16	17%	1 1 2 10 7 2 1 7 5	1997	
Shirabe et al 1997	12	13	5	13	0.8%	2 40 [1 19 4 86]	1997	
Reynolds et al 1997	23	33	15	34	17%	1 58 [1 02 2 45]	1997	
Bozzetti et al 2001	134	159	116	158	51%	1 15 [1 02 1 29]	2001	
Pacelli et al 2001	109	110	115	122	5.6%	0.96 (0.90, 1.03)	2001	-
Aiko et al 2003	15	20	15	19	2.0%	0.00 [0.00, 1.00]	2001	
Seike et al 2003	7	1/	, S Q	15	1 Q Q6	0.83 [0.01, 1.62]	2000	
Liu at al 2011	27	20	20	20	6.0%		2011	
Pork at al 2011	27 16	10	10	20	1 1 0%	0.04 [0.32, 1.10]	2011	
Listal 2012	22	22	20	20	4.170 E 406		2012	-
El et al 2012	23	23	20	20	0.470 4.00/		2012	
Pujita et al 2012 Declare et el 2014	20	70	00	00	4.370	1.07 [0.80, 1.27]	2012	
Bueleris et al 2014	39	01	28	62	2.5%	1.42 [1.01, 1.97]	2014	
Kiek et al 2014	00	84	04	83	4.2%	0.93 [0.77, 1.11]	2014	-
Huang et al 2015	31	35	23	35	3.1%	1.35 [1.03, 1.76]	2015	
Perinei et al 2016	62	102	59	101	3.6%	1.04 [0.83, 1.31]	2016	
Luo et al 2017	34	34	42	44	5.5%	1.04 [0.96, 1.13]	2017	Γ
Chen et al 2017	27	31	19	37	2.4%	1.70 [1.21, 2.39]	2017	
Wang et al 2018	66	55	51	63	5.0%	1.23 [1.09, 1.39]	2018	
Subtotal (95% CI)		1059		1091	70.0%	1.08 [1.01, 1.16]		•
Total events	840		781		=			
Heterogeneity: Tau ² = 0.01;	Chi ² = 65	.25, df=	= 22 (P <	0.0000	1); I ^z = 66	%		
Test for overall effect: $Z = 2$.	19 (P = 0.	03)						
4 4 9 9								
1.1.2 Standard Care								
Holter et al 1977	25	26	28	30	5.0%	1.03 [0.91, 1.16]	1977	+
van Eys et al 1980	7	11	6	25	0.6%	2.65 [1.16, 6.07]	1980	
Thompson et al 1981	7	9	9	12	1.5%	1.04 [0.64, 1.67]	1981	
van Eys et al 1982	19	22	17	22	3.0%	1.12 [0.84, 1.48]	1982	
Muller et al 1982	21	59	30	66	1.8%	0.78 [0.51, 1.21]	1982	
Hays et al 1983	5	5	3	5	0.8%	1.57 [0.77, 3.22]	1983	
Sandstrom et al 1993	93	150	59	150	3.5%	1.58 [1.25, 1.99]	1993	
Brennan et al 1994	37	57	24	60	2.2%	1.62 [1.13, 2.34]	1994	
Kamei et al 2005	25	27	20	21	4.7%	0.97 [0.84, 1.12]	2005	
Schmid et al 2006	11	15	7	15	1.0%	1.57 [0.84, 2.92]	2006	
Subtotal (95% CI)		381		406	24.0 %	1.22 [1.00, 1.50]		◆
Total events	250		203					
Heterogeneity: Tau ² = 0.07;	$Chi^2 = 42$.26, df=	= 9 (P < 0	.00001); l² = 79%	6		
Test for overall effect: Z = 1.	93 (P = 0.	05)						
		-						
Total (95% CI)		1440		1497	100.0%	1.11 [1.04, 1.19]		◆
Total events	1090		984					
Heterogeneity: Tau ² = 0.02;	Chi² = 11	0.99, dt	'= 32 (P ·	< 0.000	101); I ^z = 7	1%		
Test for overall effect: Z = 2.	99 (P = 0.	003)						Eavours PN Eavours EN
Test for subgroup difference	oo: Ohiž –	1.20 4	f = 1 /D =	0.253	IZ - 00.000			

Test for subgroup differences: $Chi^2 = 1.30$, df = 1 (P = 0.25), $I^2 = 23.3\%$

Figure 1.2

	EN		PN			Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight I	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
1.2.1 PEM										
Holter et al 1977	25	26	28	30	5.0%	1.03 [0.91, 1.16]	1977	+		
van Evs et al 1980	7	11	6	25	0.6%	2.65 (1.16, 6.07)	1980	· · · · · · · · · · · · · · · · · · ·		
Lim et al 1981	7	12	7	12	0.9%	1.00 (0.51, 1.97)	1981			
Sako et al 1981	30	33	34	36	4.8%	0.96 [0.84, 1.10]	1981			
Thompson et al 1981	7	9	9	12	1.5%	1 04 0 64 1 67	1981			
Muller et al 1982	21	59	30	66	1.8%	0.78 [0.51, 1.21]	1982			
van Evs et al 1982	19	22	17	22	3.0%		1982			
Von Mevenfeldt et al 1992	20	50		51	0.8%	2 55 [1 24 5 25]	1992			
Sandstrom et al 1993	93	150	59	150	3.5%	1 58 [1 25 1 99]	1993	_ _		
Reynolds et al 1997	23	33	15	34	17%	1 58 [1 02 2 45]	1997			
Bozzetti et al 2001	134	159	116	158	51%	1 15 [1 02 1 29]	2001			
Park et al 2012	16	18	10	20	4 1 %	0.94 (0.77, 1.13)	2001			
Klek et al 2012	00	94	64	20	1 7%	0.34 [0.11, 1.13]	2012			
Subtotal (95% CI)	00	666	04	699	36.9%	1.12 [0.98, 1.28]	2014	▲		
Total evente	462		112					•		
Hotorogonoity: Tou ² – 0.02:	402 Chiž – 42	07 df-	- 12/D -	0 0001)· IZ = 70%					
Test for sucrell effect: 7 = 1	CHI = 43. 6070 = 01	.97, ui - 003	- 12 (F S	0.0001),1 = 7.3.%					
Test for overall effect. $Z = 1$.	00 (F = 0.1	09)								
1.2.2 No DEM										
Lieve et al 4002	-	-	-	-	0.00	4 57 10 77 0 001	4000			
Hays et al 1983	10	2	3	5	0.8%	1.57 [0.77, 3.22]	1983			
Hamaoul et al 1990	10	11	8	8	3.1%	0.93 [0.71, 1.21]	1990			
Iovinelli et al 1993	19	24	20	24	3.1%	0.95 [0.72, 1.25]	1993			
Brennan et al 1994	37	57	24	60	2.2%	1.62 [1.13, 2.34]	1994			
Shirabe et al 1997	12	13	5	13	0.8%	2.40 [1.19, 4.86]	1997			
Sand et al 1997	10	13	11	16	1.7%	1.12 [0.72, 1.75]	1997			
Pacelli et al 2001	108	119	115	122	5.6%	0.96 [0.90, 1.03]	2001	*		
Aiko et al 2003	15	20	15	19	2.4%	0.95 [0.67, 1.34]	2003			
Kamei et al 2005	25	27	20	21	4.7%	0.97 [0.84, 1.12]	2005			
Schmid et al 2006	11	15	7	15	1.0%	1.57 [0.84, 2.92]	2006			
Liu et al 2011	27	28	28	30	5.0%	1.03 [0.92, 1.16]	2011	+		
Seike et al 2011	7	14	9	15	0.9%	0.83 [0.43, 1.62]	2011			
Li et al 2012	23	23	20	20	5.4%	1.00 [0.92, 1.09]	2012	+		
Fujita et al 2012	60	76	65	88	4.3%	1.07 [0.90, 1.27]	2012			
Boelens et al 2014	39	61	28	62	2.5%	1.42 [1.01, 1.97]	2014			
Huang et al 2015	31	35	23	35	3.1%	1.35 [1.03, 1.76]	2015			
Perinel et al 2016	62	102	59	101	3.6%	1.04 [0.83, 1.31]	2016			
Luo et al 2017	34	34	42	44	5.5%	1.04 [0.96, 1.13]	2017	+		
Chen et al 2017	27	31	19	37	2.4%	1.70 [1.21, 2.39]	2017			
Wang et al 2018	66	66	51	63	5.0%	1.23 [1.09, 1.39]	2018			
Subtotal (95% CI)		774		798	63.1%	1.11 [1.02, 1.20]		◆		
Total events	628		572							
Heterogeneity: Tau ² = 0.02;	Chi ² = 63.	.19, df:	= 19 (P <	0.0000	l1); I ² = 709	6				
Test for overall effect: Z = 2.46 (P = 0.01)										
Total (95% CI)		1440		1497	100.0 %	1.11 [1.04, 1.19]		•		
Total events	1090		984							
Heterogeneity: Tau ² = 0.02;	Chi ² = 11	0.99, d	f= 32 (P -	< 0.000	i01); i² = 71	%				
Test for overall effect: Z = 2.	99 (P = 0.)	003)	-					U.Z U.S 1 Z 5 Eavoure PN Eavoure EN		
Test for subgroup differences: Chi ² = 0.02, df = 1 (P = 0.89), i ² = 0% Favours PN Favours EN										

Figure 1.3

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.3.1 Children								
van Eys et al 1980	7	11	6	25	0.6%	2.65 [1.16, 6.07]	1980	· · · · · · · · · · · · · · · · · · ·
van Eys et al 1982	19	22	17	22	3.0%	1.12 [0.84, 1.48]	1982	
Hays et al 1983	5	5	3	5	0.8%	1.57 [0.77, 3.22]	1983	
Schmid et al 2006	11	15	7	15	1.0%	1.57 [0.84, 2.92]	2006	
Subtotal (95% CI)		53		67	5.4%	1.47 [1.00, 2.16]		
Total events	42		33					
Heterogeneity: Tau ² = 0.07;	Chi ² = 5.4	6. df=	3 (P = 0.1	(4); I ² =	45%			
Test for overall effect: Z = 1.	98 (P = 0.I	05)						
	`	·						
1.3.2 Adults								
Holter et al 1977	25	26	28	30	5.0%	1.03 [0.91, 1.16]	1977	+
Thompson et al 1981	7	9	9	12	1.5%	1.04 [0.64, 1.67]	1981	
Sako et al 1981	30	33	34	36	4.8%	0.96 [0.84, 1.10]	1981	-
Lim et al 1981	7	12	7	12	0.9%	1.00 (0.51, 1.97)	1981	
Muller et al 1982	21	59	30	66	1.8%	0.78 [0.51, 1.21]	1982	
Hamaoui et al 1990	10	11	8	8	3.1%	0.93 [0.71, 1.21]	1990	
Von Mevenfeldt et al 1992	20	50	8	51	0.8%	2.55 [1.24, 5.25]	1992	·
lovinelli et al 1993	19	24	20	24	3.1%	0.95 [0.72, 1.25]	1993	
Sandstrom et al 1993	93	150	59	150	3.5%	1.58 (1.25, 1.99)	1993	
Brennan et al 1994	37	57	24	60	2.2%	1.62 [1.13, 2.34]	1994	
Revnolds et al 1997	23	33	15	34	1.7%	1.58 [1.02, 2.45]	1997	
Sand et al 1997	10	13	11	16	1.7%	1.12 [0.72, 1.75]	1997	
Shirabe et al 1997	12	13	5	13	0.8%	2.40 [1.19, 4.86]	1997	
Bozzetti et al 2001	134	159	116	158	5.1%	1.15 [1.02, 1.29]	2001	
Pacelli et al 2001	108	119	115	122	5.6%	0.96 (0.90, 1.03)	2001	-
Aiko et al 2003	15	20	15	19	2.4%	0.95 [0.67, 1.34]	2003	
Kamei et al 2005	25	27	20	21	4.7%	0.97 [0.84, 1.12]	2005	
Seike et al 2011	7	14	9	15	0.9%	0.83 [0.43, 1.62]	2011	
Liu et al 2011	27	28	28	30	5.0%	1.03 [0.92, 1.16]	2011	+
Li et al 2012	23	23	20	20	5.4%	1.00 (0.92, 1.09)	2012	+
Park et al 2012	16	18	19	20	4.1%	0.94 [0.77, 1.13]	2012	
Fujita et al 2012	60	76	65	88	4.3%	1.07 [0.90, 1.27]	2012	
Boelens et al 2014	39	61	28	62	2.5%	1.42 [1.01, 1.97]	2014	
Klek et al 2014	60	84	64	83	4.2%	0.93 [0.77, 1.11]	2014	
Huang et al 2015	31	35	23	35	3.1%	1.35 [1.03, 1.76]	2015	
Perinel et al 2016	62	102	59	101	3.6%	1.04 [0.83, 1.31]	2016	_ _
Luo et al 2017	34	34	42	44	5.5%	1.04 [0.96, 1.13]	2017	+
Chen et al 2017	27	31	19	37	2.4%	1.70 [1.21, 2.39]	2017	
Wang et al 2018	66	66	51	63	5.0%	1.23 [1.09, 1.39]	2018	
Subtotal (95% CI)		1387		1430	94.6%	1.09 [1.02, 1.17]		•
Total events	1048		951					
Heterogeneity: Tau ² = 0.02;	Chi ² = 98	.88. df:	= 28 (P <	0.0000	I1): I ² = 729	б		
Test for overall effect: Z = 2.	59 (P = 0.	010)	,					
Total (95% CI)		1440		1497	100.0%	1.11 [1.04, 1.19]		•
Total events	1090		984					
Heterogeneity: Tau ² = 0.02;	Chi ² = 11	0.99, d	f= 32 (P ·	< 0.000	101); I ^z = 71	%		
Test for overall effect: $Z = 2$.	99 (P = 0.	003)						Favours PN Favours EN
Test for subgroup difference	es: Chi ^z =	2.23, 0	lf = 1 (P =	0.14),	I ² = 55.1%			

Figure 1. No infection for enteral nutrition (EN) and parenteral nutrition (PN) patients **1.1** Analyses by EN – tube feeding and standard care **1.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **1.3** Analyses by age of population – children and adults

Study name		Cum	ulative s	tatistics		Cumulative mh risk ratio (95% CI)	
	Point	Lower limit	Upper limit	Z-Value	p-Value		
Holter et al 1977	1.030	0.754	1.407	0.187	0.851		
van Eys et al 1980	1.145	0.854	1.536	0.907	0.365		
Thompson et al 1981	1.121	0.865	1.453	0.862	0.389		— —
Sako et al 1981	1.054	0.863	1.288	0.516	0.606		
Lim et al 1981	1.050	0.866	1.275	0.498	0.619		— —
Muller et al 1982	1.013	0.845	1.215	0.144	0.886		—— — ——
van Eys et al 1982	1.030	0.873	1.216	0.355	0.723		— 4 —
Havs et al 1983	1.050	0.893	1.234	0.587	0.557		
Hamaoui et al 1990	1.031	0.888	1.197	0.396	0.692		
Von Meyenfeldt et al 1992	1.065	0.919	1.233	0.836	0.403		
Sandstrom et al 1993	1.123	0.980	1.287	1.664	0.096		++
Iovinelli et al 1993	1.103	0.970	1.255	1.490	0.136		
Brennan et al 1994	1.134	1.002	1.284	1.984	0.047		
Shirabe et al 1997	1.156	1.023	1.307	2.322	0.020		
Sand et al 1997	1.154	1.024	1.301	2.356	0.018		
Reynolds et al 1997	1.172	1.043	1.317	2.675	0.007		
Bozzetti et al 2001	1.169	1.049	1.304	2.812	0.005		-+
Pacelli et al 2001	1.142	1.031	1.265	2.551	0.011		
Aiko et al 2003	1.132	1.025	1.250	2.437	0.015		
Kamei et al 2005	1.117	1.015	1.228	2.276	0.023		_+_
Schmid et al 2006	1.124	1.023	1.235	2.433	0.015		-+
Seike et al 2011	1.118	1.019	1.228	2.349	0.019		
Liu et al 2011	1.111	1.016	1.215	2.309	0.021		
Park et al 2012	1.099	1.008	1.199	2.140	0.032		⊢ +−
Fujita et al 2012	1.097	1.009	1.193	2.169	0.030		 −+−
Boelens et al 2014	1.107	1.020	1.202	2.422	0.015		-+-
Klek et al 2014	1.096	1.012	1.187	2.248	0.025		-+-
Huang et al 2015	1.105	1.022	1.195	2.501	0.012		_+_
Perinel et al 2016	1.102	1.021	1.190	2.490	0.013		_+_
Luo et al 2017	1.099	1.020	1.183	2.482	0.013		-+-
Chen et al 2017	1.111	1.033	1.196	2.830	0.005		-+-
Wang et al 2018	1.118	1.041	1.200	3.057	0.002		-+-
-	1.118	1.041	1.200	3.057	0.002		
						0.5	1
							Favours PN Favours EN

Figure 2. No infection for enteral (EN) and parenteral nutrition (PN) patients, over time

Figure 3.1

	EN		PN			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl			
3.1.1 Tube Feeding											
Sako et al 1981	33	33	34	36	6.4%	1.06 [0.96, 1.16]	1981	+			
Lim et al 1981	12	12	11	12	2.7%	1.09 [0.87, 1.36]	1981				
Hamaoui et al 1990	10	11	7	8	1.6%	1.04 [0.75, 1.43]	1990				
Von Meyenfeldt et al 1992	50	50	49	51	7.6%	1.04 [0.97, 1.11]	1992	+			
lovinelli et al 1993	24	24	17	24	2.2%	1.40 [1.08, 1.82]	1993				
Reynolds et al 1997	30	33	34	34	5.5%	0.91 [0.81, 1.03]	1997				
Sand et al 1997	13	13	16	16	5.1%	1.00 [0.88, 1.14]	1997				
Shirabe et al 1997	13	13	13	13	4.7%	1.00 [0.87, 1.15]	1997				
Bozzetti et al 2001	103	159	136	158	5.1%	0.75 [0.66, 0.86]	2001	_			
Liu et al 2011	27	28	28	30	5.5%	1.03 [0.92, 1.16]	2011				
Seike et al 2011	14	14	15	15	5.2%	1.00 [0.88, 1.14]	2011				
Park et al 2012	14	18	20	20	2.2%	0.78 [0.60, 1.01]	2012				
Huang et al 2015	20	35	32	35	1.7%	0.63 [0.46, 0.85]	2015				
Li et al 2015	107	136	98	136	4.9%	1.09 [0.95, 1.25]	2015				
Subtotal (95% CI)		579		588	60.4 %	0.98 [0.90, 1.06]		•			
Total events	470		510								
Heterogeneity: Tau ² = 0.02;	Chi ² = 55	.44, df:	= 13 (P <	0.0000	l1); l² = 77	7%					
Test for overall effect: Z = 0.	53 (P = 0.	60)									
3.1.2 Standard Care											
Holter et al 1977	26	26	30	30	7.6%	1.00 [0.93, 1.07]	1977				
Thompson et al 1981	9	9	11	12	2.4%	1.07 [0.84, 1.37]	1981				
Ghavimi et al 1982	13	14	9	11	1.6%	1.13 [0.83, 1.55]	1982				
Donaldson et al 1982	4	13	3	12	0.1%	1.23 [0.34, 4.40]	1982	· · · · · ·			
Muller et al 1982	59	59	64	66	8.2%	1.03 [0.98, 1.09]	1982				
Smith et al 1992	6	6	5	6	0.9%	1.18 [0.76, 1.83]	1992				
Sandstrom et al 1993	141	150	138	150	7.8%	1.02 [0.96, 1.09]	1993				
Brennan et al 1994	57	57	58	60	8.0%	1.03 [0.98, 1.09]	1994	+			
Kamei et al 2005	23	27	19	21	3.0%	0.94 [0.76, 1.16]	2005				
Subtotal (95% CI)		361		368	39.6%	1.02 [1.00, 1.05]		•			
Total events	338		337								
Heterogeneity: Tau ² = 0.00;	Chi ² = 2.3	84, df =	8 (P = 0.9	97); I ² =	0%						
Test for overall effect: Z = 1.	.62 (P = 0.	10)									
T-1-1 (05% OD				0.5.5	100.00	4 00 10 00 1 000		1			
Total (95% CI)		940		956	100.0%	1.00 [0.96, 1.05]		₹			
Total events	808		847								
Heterogeneity: Tau ² = 0.01;	Chi² = 59	.77, df	= 22 (P <	0.0001); I^z = 639	Хо		0.5 0.7 1 1.5 2			
Test for overall effect: $Z = 0$.	.01 (P = 0.	99)						Favours PN Favours EN			
Test for subgroup differenc	es: Chi²=	1.11, 0	lf = 1 (P =	0.29),	I ² = 10.29	6					

Figure 3.2

	EN		PN			Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
3.2.1 PEM										
Holter et al 1977	26	26	30	30	7.6%	1.00 [0.93, 1.07]	1977	-+-		
Sako et al 1981	33	33	34	36	6.4%	1.06 [0.96, 1.16]	1981	-+		
Thompson et al 1981	9	9	11	12	2.4%	1.07 [0.84, 1.37]	1981			
Lim et al 1981	12	12	11	12	2.7%	1.09 [0.87, 1.36]	1981			
Muller et al 1982	59	59	64	66	8.2%	1.03 [0.98, 1.09]	1982			
Donaldson et al 1982	4	13	3	12	0.1%	1.23 [0.34, 4.40]	1982	· · · · · · · · · · · · · · · · · · ·		
Von Meyenfeldt et al 1992	50	50	49	51	7.6%	1.04 [0.97, 1.11]	1992	-+ -		
Smith et al 1992	6	6	5	6	0.9%	1.18 [0.76, 1.83]	1992			
Sandstrom et al 1993	141	150	138	150	7.8%	1.02 [0.96, 1.09]	1993			
Reynolds et al 1997	30	33	34	34	5.5%	0.91 [0.81, 1.03]	1997			
Bozzetti et al 2001	103	159	136	158	5.1%	0.75 [0.66, 0.86]	2001			
Park et al 2012	14	18	20	20	2.2%	0.78 [0.60, 1.01]	2012			
Subtotal (95% CI)		568		587	56.6%	0.98 [0.92, 1.05]		+		
Total events	487		535							
Heterogeneity: Tau ² = 0.01;	Chi ² = 49.	.70, df:	= 11 (P <	0.0000	1); I ² = 78	3%				
Test for overall effect: Z = 0.	50 (P = 0.)	62)								
3.2.2 No DEM										
Chovimi et al 1002	10	1.4	0	11	1 606	1 1 2 10 0 2 1 6 51	1000			
Homooui et al 1962	10	14	37		1.070	1.13 [0.63, 1.33]	1902			
haillaoui et al 1990	24	24	17	0 24	1.070	1.04 [0.70, 1.40]	1990			
Pronnon et al 1993	24 57	57	50	24 60	2.2.70		1004			
Condict of 1994	12	10	16	16	6.0%	1.03 [0.30, 1.03]	1007			
Sand et al 1997 Shiraha at al 1997	13	13	13	13	1 7%		1007			
Vamei et al 2005	23	27	10	21	3.0%	0.04/0.76/1.16	2005			
Seike et al 2003	14	11	15	15	5.0%		2003			
Liu et al 2011	27	28	28	30	5.5%	1.00 [0.00, 1.14]	2011	.		
Huang et al 2015	20	35	32	35	1 7%	0.63 (0.46, 0.85)	2011	←		
Lietal 2015	107	136	98	136	4 9%		2015	_ _		
Subtotal (95% CI)	101	372		369	43.4%	1.02 [0.96, 1.09]	2010	•		
Total events	321		312			. , .		Ĩ		
Heterogeneity: $Tau^2 = 0.00^{\circ}$	$Chi^2 = 17$	95 df:	= 10 (P =							
Test for overall effect: Z = 0.	66 (P = 0.)	51)								
Total (95% CI)		940		956	100.0%	1.00 [0.96, 1.05]		•		
Total events	808		847							
Heterogeneity: Tau ² = 0.01;	Chi² = 59	.77, df:	= 22 (P <	0.0001); I ² = 639	6				
Test for overall effect: Z = 0.	01 (P = 0.)	99)						Favours PN Favours EN		
Test for subgroup difference	es: Chi ^z =	0.65, 0	lf = 1 (P =	0.42),	I² = 0%					

Figure 3.3

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
3.3.1 Children								
Donaldson et al 1982	4	13	3	12	0.1%	1.23 [0.34, 4.40]	1982	· · · · · · · · · · · · · · · · · · ·
Ghavimi et al 1982	13	14	9	11	1.6%	1.13 [0.83, 1.55]	1982	
Subtotal (95% CI)		27		23	1.7%	1.14 [0.84, 1.55]		
Total events	17		12					
Heterogeneity: Tau ² = 0.00;	$Chi^{2} = 0.0$	2, df=	1 (P = 0.8	38); I ^z =	0%			
Test for overall effect: Z = 0.	84 (P = 0	40)						
3.3.2 Adults								
Holter et al 1977	26	26	30	30	7.6%	1.00 [0.93, 1.07]	1977	-+-
Thompson et al 1981	9	9	11	12	2.4%	1.07 [0.84, 1.37]	1981	
Sako et al 1981	33	33	34	36	6.4%	1.06 [0.96, 1.16]	1981	-+
Lim et al 1981	12	12	11	12	2.7%	1.09 [0.87, 1.36]	1981	
Muller et al 1982	59	59	64	66	8.2%	1.03 [0.98, 1.09]	1982	
Hamaoui et al 1990	10	11	7	8	1.6%	1.04 [0.75, 1.43]	1990	
Smith et al 1992	6	6	5	6	0.9%	1.18 [0.76, 1.83]	1992	
Von Meyenfeldt et al 1992	50	50	49	51	7.6%	1.04 [0.97, 1.11]	1992	+
lovinelli et al 1993	24	24	17	24	2.2%	1.40 [1.08, 1.82]	1993	· · · · · · · · · · · · · · · · · · ·
Sandstrom et al 1993	141	150	138	150	7.8%	1.02 [0.96, 1.09]	1993	
Brennan et al 1994	57	57	58	60	8.0%	1.03 [0.98, 1.09]	1994	
Shirabe et al 1997	13	13	13	13	4.7%	1.00 [0.87, 1.15]	1997	
Reynolds et al 1997	30	33	34	34	5.5%	0.91 [0.81, 1.03]	1997	
Sand et al 1997	13	13	16	16	5.1%	1.00 [0.88, 1.14]	1997	
Bozzetti et al 2001	103	159	136	158	5.1%	0.75 [0.66, 0.86]	2001	
Kamei et al 2005	23	27	19	21	3.0%	0.94 [0.76, 1.16]	2005	
Liu et al 2011	27	28	28	30	5.5%	1.03 [0.92, 1.16]	2011	+
Seike et al 2011	14	14	15	15	5.2%	1.00 [0.88, 1.14]	2011	+
Park et al 2012	14	18	20	20	2.2%	0.78 [0.60, 1.01]	2012	
Li et al 2015	107	136	98	136	4.9%	1.09 [0.95, 1.25]	2015	+
Huang et al 2015	20	35	32	35	1.7%	0.63 [0.46, 0.85]	2015	·
Subtotal (95% CI)		913		933	98.3%	1.00 [0.95, 1.04]		•
Total events	791		835					
Heterogeneity: Tau ² = 0.01;	Chi ² = 60.	.56, df=	= 20 (P <	0.0000	1); l² = 67	%		
Test for overall effect: $Z = 0$.	11 (P = 0.9	92)						
Total (95% CI)		940		956	100.0%	1.00 [0.96, 1.05]		
Total events	808		847					
Heterogeneity: Tau ² = 0.01;	Chi ² = 59.	.77, df=	= 22 (P <	0.0001); I^z = 63%	6		
Test for overall effect: $Z = 0$.	01 (P = 0.9	99)						0.7 0.85 F Favours EN
Test for subaroun difference	es: Chi ^z =	0.72 d	f = 1 (P =	0.40)	I ² = 0%			

Test for subgroup differences: $Chi^2 = 0.72$, df = 1 (P = 0.40), $I^2 = 0\%$ **Figure 3.** No nutrition support complications for enteral nutrition (EN) and parenteral nutrition (PN) patients **3.1** Analyses by EN – tube feeding and standard care **3.2** Analyses by nutrition status - protein energy malnutrition (PEM) and no PEM **3.3** Analyses by age of population - children and adults

<u>Study name</u>		Cum	llative st	atistics		Cumulative mh risk ratio (95% CI)
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Thompson et al 1980	1.074	0.797	1.446	0.469	0.639	
Sako et al 1981	1.062	0.901	1.252	0.715	0.475	
Lim et al 1981	1.068	0.926	1.232	0.908	0.364	
Muller et al 1982	1.053	0.942	1.178	0.912	0.362	
Ghavimi et al 1982	1.060	0.953	1.180	1.077	0.281	
Donaldson et al 1982	1.062	0.954	1.181	1.099	0.272	
Hamaoui et al 1990	1.060	0.957	1.174	1.113	0.266	
Von Meyenfeldt et al 199	2 1.055	0.965	1.154	1.176	0.240	
Smith et al 1992	1.059	0.970	1.157	1.285	0.199	
Sandstrom et al 1993	1.052	0.972	1.139	1.258	0.208	
Iovinelli et al 1993	1.070	0.991	1.156	1.733	0.083	
Brennan et al 1994	1.065	0.992	1.143	1.735	0.083	
Reynolds et al 1997	1.048	0.980	1.121	1.366	0.172	
Bozzetti et al 2001	1.018	0.955	1.085	0.544	0.587	
Kamei et al 2005	1.014	0.952	1.079	0.429	0.668	
Liu et al 2011	1.015	0.956	1.078	0.498	0.618	
Park et al 2012	1.006	0.949	1.067	0.197	0.843	
Li et al 2015	1.011	0.956	1.071	0.392	0.695	
Huang et al 2015	0.999	0.945	1.057	-0.034	0.973	
e	0.999	0.945	1.057	-0.034	0.973	
						0.5 1 2
						Favours PN Favours FN
Figure 4. No nutrition patients, over time	on supj	port co	mplica	tions fo	r enteral	(EN) and parenteral nutrition (PN

Figure 5.1

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
5.1.1 Tube Feeding								
Sako et al 1981	27	33	30	36	5.2%	0.98 [0.79, 1.22]	1981	
Lim et al 1981	5	12	9	12	0.6%	0.56 [0.26, 1.17]	1981	•
Heylen et al 1987	10	10	10	10	6.7%	1.00 [0.83, 1.20]	1987	_
Hamaoui et al 1990	11	11	8	8	6.0%	1.00 [0.82, 1.22]	1990	
Von Meyenfeldt et al 1992	44	50	45	51	9.1%	1.00 [0.86, 1.15]	1992	
lovinelli et al 1993	23	24	22	24	8.8%	1.05 [0.90, 1.21]	1993	
Sand et al 1997	10	13	13	16	2.0%	0.95 [0.65, 1.38]	1997	
Shirabe et al 1997	13	13	13	13	9.1%	1.00 [0.87, 1.15]	1997	
Pacelli et al 2001	74	119	74	122	5.9%	1.03 [0.84, 1.25]	2001	
Bozzetti et al 2001	139	159	128	158	13.3%	1.08 [0.98, 1.19]	2001	+
Aiko et al 2003	16	20	15	19	2.8%	1.01 [0.74, 1.39]	2003	
Fujita et al 2012	64	76	61	88	7.4%	1.21 [1.03, 1.44]	2012	
Klek et al 2014	55	84	54	83	5.1%	1.01 [0.81, 1.26]	2014	
Perinel et al 2016	23	102	36	101	1.5%	0.63 [0.41, 0.99]	2016	·
Subtotal (95% CI)		726		741	83.6%	1.03 [0.98, 1.08]		•
Total events	514		518					
Heterogeneity: Tau ² = 0.00;	Chi ² = 13	.33, df:	= 13 (P =	0.42);1	z =2%			
Test for overall effect: Z = 1.	.23 (P = 0.	22)						
5.1.2 Standard Care								
Holter et al 1977	21	26	26	30	4.6%	0.93 [0.74, 1.18]	1977	
Thompson et al 1981	8	9	10	12	2.5%	1.07 [0.76, 1.50]	1981	
Muller et al 1982	40	59	55	66	5.6%	0.81 [0.66, 1.00]	1982	
Brennan et al 1994	44	57	33	60	3.7%	1.40 [1.07, 1.84]	1994	
Subtotal (95% CI)		151		168	16.4%	1.02 [0.80, 1.30]		
Total events	113		124					
Heterogeneity: Tau ² = 0.04;	Chi² = 10	.65, df:	= 3 (P = 0	.01); I²	= 72%			
Test for overall effect: Z = 0.	.16 (P = 0.	87)						
Total (95% CI)		877		909	100.0%	1 02 [0 96 1 09]		
Total evente	607	011	642	303	.00.070	102 [0.30, 1.00]		T
Hotorogonoity: Tou? = 0.00:	027 Chia - 22	06 46	042	0.4.3\	z _ 200			
Test for everall effect: 7 = 9	CHE = 23	.00, UI : 66)	= 17 (P =	0.12),1	-= 29%			0.7 0.85 1 1.2 1.5
Test for overall effect. $Z = 0$.	.09 (P = 0. 	Favours PN Favours EN						
restion subdroub alletenc	es. unin=	0.01,0	n = 1 (P =	0.93),	1 = 0%			

Figure 5.2

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
5.2.1 PEM								
Holter et al 1977	21	26	26	30	4.6%	0.93 [0.74, 1.18]	1977	
Sako et al 1981	27	33	30	36	5.2%	0.98 [0.79, 1.22]	1981	
Thompson et al 1981	8	9	10	12	2.5%	1.07 [0.76, 1.50]	1981	
Lim et al 1981	5	12	9	12	0.6%	0.56 [0.26, 1.17]	1981	←
Muller et al 1982	40	59	55	66	5.6%	0.81 [0.66, 1.00]	1982	
Von Meyenfeldt et al 1992	44	50	45	51	9.1%	1.00 [0.86, 1.15]	1992	
Bozzetti et al 2001	139	159	128	158	13.3%	1.08 [0.98, 1.19]	2001	+
Klek et al 2014	55	84	54	83	5.1%	1.01 [0.81, 1.26]	2014	
Subtotal (95% CI)		432		448	46.0%	0.99 [0.91, 1.07]		-
Total events	339		357					
Heterogeneity: Tau ² = 0.00;	Chi² = 9.5	i1, df=	7 (P = 0.2	22); I ² =	26%			
Test for overall effect: Z = 0.	35 (P = 0.)	73)						
5.2.2 NO PEM								
Heylen et al 1987	10	10	10	10	6.7%	1.00 [0.83, 1.20]	1987	
Hamaoui et al 1990	11	11	8	8	6.0%	1.00 [0.82, 1.22]	1990	
lovinelli et al 1993	23	24	22	24	8.8%	1.05 [0.90, 1.21]	1993	
Brennan et al 1994	44	57	33	60	3.7%	1.40 [1.07, 1.84]	1994	
Sand et al 1997	10	13	13	16	2.0%	0.95 [0.65, 1.38]	1997	
Shirabe et al 1997	13	13	13	13	9.1%	1.00 [0.87, 1.15]	1997	
Pacelli et al 2001	74	119	74	122	5.9%	1.03 [0.84, 1.25]	2001	
Aiko et al 2003	16	20	15	19	2.8%	1.01 [0.74, 1.39]	2003	
Fujita et al 2012	64	76	61	88	7.4%	1.21 [1.03, 1.44]	2012	
Perinel et al 2016	23	102	36	101	1.5%	0.63 [0.41, 0.99]	2016	
Subtotal (95% CI)		445		461	54.0%	1.05 [0.96, 1.14]		-
Total events	288		285					
Heterogeneity: Tau ² = 0.01;	Chi ² = 13.	.64, df:	= 9 (P = 0	.14); I²	= 34%			
Test for overall effect: Z = 1.	06 (P = 0.)	29)						
Total (95% CI)		877		909	100.0%	1.02 [0.96, 1.08]		•
Total events	627		642			- / -		ſ
Heterogeneity: $Tau^2 = 0.00^{\circ}$	Chi ² = 23	86.df:	= 17 (P =	0.12) I	²= 29%			
Test for overall effect: $7 = 0$	59 (P = 0	55) 55)			20.0			0.7 0.85 1 1.2 1.5
Test for subgroup differenc	es: Chi ² =	1.00. c	lf = 1 (P =	0.32).	l² = 0%			Favours PN Favours EN

Figure 5.3

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
5.3.1 Children								
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not applicab	le							
Test for overall effect: Not a	oplicable							
5.3.2 Adults								
Holter et al 1977	21	26	26	30	4.6%	0.93 [0.74, 1.18]	1977	
Thompson et al 1981	8	9	10	12	2.5%	1.07 [0.76, 1.50]	1981	
Lim et al 1981	5	12	9	12	0.6%	0.56 [0.26, 1.17]	1981	•
Sako et al 1981	27	33	30	36	5.2%	0.98 [0.79, 1.22]	1981	
Muller et al 1982	40	59	55	66	5.6%	0.81 [0.66, 1.00]	1982	
Heylen et al 1987	10	10	10	10	6.7%	1.00 [0.83, 1.20]	1987	
Hamaoui et al 1990	11	11	8	8	6.0%	1.00 [0.82, 1.22]	1990	
Von Meyenfeldt et al 1992	44	50	45	51	9.1%	1.00 [0.86, 1.15]	1992	
lovinelli et al 1993	23	24	22	24	8.8%	1.05 [0.90, 1.21]	1993	
Brennan et al 1994	44	57	33	60	3.7%	1.40 [1.07, 1.84]	1994	·
Sand et al 1997	10	13	13	16	2.0%	0.95 [0.65, 1.38]	1997	
Shirabe et al 1997	13	13	13	13	9.1%	1.00 [0.87, 1.15]	1997	
Bozzetti et al 2001	139	159	128	158	13.3%	1.08 [0.98, 1.19]	2001	+
Pacelli et al 2001	74	119	74	122	5.9%	1.03 [0.84, 1.25]	2001	
Aiko et al 2003	16	20	15	19	2.8%	1.01 [0.74, 1.39]	2003	
Fujita et al 2012	64	76	61	88	7.4%	1.21 [1.03, 1.44]	2012	
Klek et al 2014	55	84	54	83	5.1%	1.01 [0.81, 1.26]	2014	
Perinel et al 2016	23	102	36	101	1.5%	0.63 [0.41, 0.99]	2016	·
Subtotal (95% CI)		877		909	100.0%	1.02 [0.96, 1.08]		•
Total events	627		642					
Heterogeneity: Tau ² = 0.00;	Chi ² = 23	.86, df:	= 17 (P =	0.12);1	≃ = 29%			
Test for overall effect: Z = 0.	59 (P = 0.	55)						
Total (05% CI)		077		000	100.0%	1021006 1001		
Total (95% CI)		877		909	100.0%	1.02 [0.96, 1.08]		Ŧ
lotal events	627		642					
Heterogeneity: lauf = 0.00;	Cnif = 23	.86, df:	= 17 (P =	0.12);1	* = 29%			0.7 0.85 1 1.2 1.5
Test for overall effect: $Z = 0.1$	59 (P = 0.	55)						Favours PN Favours EN
l est for subgroup difference	es: Not ap	plicabl	le					

Figure 5. No major complications for enteral nutrition (EN) and parenteral nutrition (PN) patients **5.1** Analyses by EN – tube feeding and standard care **5.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **5.3** Analyses by age of population – children and adults



Figure 6. No major complications for enteral (EN) and parenteral nutrition (PN) patients, over time

Figure 7.1

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
7.1.1 Tube Feeding								
Sako et al 1981	33	33	33	36	1.4%	1.09 [0.97, 1.22]	1981	
Lim et al 1981	10	12	11	12	0.2%	0.91 [0.67, 1.23]	1981	
Rickard et al 1983	6	6	10	10	0.3%	1.00 [0.78, 1.27]	1983	
Hamaoui et al 1990	10	11	8	8	0.2%	0.93 [0.71, 1.21]	1990	
Von Meyenfeldt et al 1992	46	50	49	51	1.8%	0.96 [0.87, 1.06]	1992	
lovinelli et al 1993	24	24	24	24	2.8%	1.00 [0.92, 1.08]	1993	
Reynolds et al 1997	31	33	33	34	1.6%	0.97 [0.87, 1.07]	1997	
Shirabe et al 1997	13	13	13	13	0.9%	1.00 [0.87, 1.15]	1997	
Sand et al 1997	13	13	15	16	0.5%	1.06 [0.88, 1.26]	1997	
Pacelli et al 2001	112	119	119	122	6.2%	0.96 [0.92, 1.02]	2001	
Jiang et al 2003	20	20	20	20	1.9%	1.00 [0.91, 1.10]	2003	
Aiko et al 2003	20	20	19	19	1.9%	1.00 [0.91, 1.10]	2003	
Hyltander et al 2005	26	26	27	27	3.4%	1.00 [0.93, 1.07]	2005	
Liu et al 2011	28	28	30	30	4.0%	1.00 [0.94, 1.07]	2011	
Park et al 2012	18	18	20	20	1.8%	1.00 [0.91, 1.10]	2012	
Fujita et al 2012	74	76	86	88	7.3%	1.00 [0.95, 1.05]	2012	-
Li et al 2012	23	23	20	20	2.2%	1.00 [0.92, 1.09]	2012	
Boelens et al 2014	61	61	62	62	17.5%	1.00 [0.97, 1.03]	2014	+
Dmytriiev et al 2014	60	60	52	52	14.4%	1.00 [0.97, 1.04]	2014	+
Klek et al 2014	82	84	82	83	10.4%	0.99 [0.95, 1.03]	2014	
Perinel et al 2016	93	103	98	101	3.4%	0.93 [0.87, 1.00]	2016	
Harvey et al 2016	48	80	36	66	0.2%	1.10 [0.83, 1.46]	2016	
Chen et al 2017	31	31	36	37	2.9%	1.02 [0.95, 1.11]	2017	
Subtotal (95% CI)		944		951	87.0 %	0.99 [0.98, 1.01]		•
Total events	882		903					
Heterogeneity: Tau ² = 0.00;	Chi ² = 10	.61, df=	= 22 (P =	0.98); I	²=0%			
Test for overall effect: Z = 0.	86 (P = 0.	39)						
7.1.2 Standard Care								
Holter et al 1977	24	26	28	30	0.8%	0.99 [0.85, 1.15]	1977	
van Eys et al 1980	9	11	18	25	0.1%	1.14 [0.78, 1.65]	1980	
Thompson et al 1981	9	9	12	12	0.5%	1.00 [0.84, 1.20]	1981	
Donaldson et al 1982	12	13	11	12	0.3%	1.01 [0.80, 1.27]	1982	
Ghavimi et al 1982	10	14	8	11	0.1%	0.98 [0.60, 1.60]	1982	
Muller et al 1982	48	59	63	66	1.0%	0.85 [0.75, 0.97]	1982	
Hays et al 1983	5	5	5	5	0.1%	1.00 [0.71, 1.41]	1983	
Smith et al 1992	5	6	6	6	0.1%	0.85 [0.55, 1.31]	1992	•
Sandstrom et al 1993	140	150	138	150	4.3%	1.01 [0.95, 1.08]	1993	
Brennan et al 1994	56	57	56	60	3.0%	1.05 [0.98, 1.14]	1994	
Kamei et al 2005	27	27	21	21	2.7%	1.00 [0.92, 1.08]	2005	
Subtotal (95% CI)		377		398	13.0%	1.00 [0.97, 1.04]		•
Total events	345		366					
Heterogeneity: Tau ² = 0.00;	Chi ² = 9.1	1, df =	10 (P = 0	.52); I²	= 0%			
Test for overall effect: Z = 0.	21 (P = 0.	83)						
		100						
Total (95% Cl)		1321		1349	100.0%	1.00 [0.98, 1.01]		•
Total events	1227		1269					
Heterogeneity: Tau ² = 0.00;	Chi ² = 19	.70, df=	= 33 (P =	0.97);1	² =0%			
Test for overall effect: Z = 0.	73 (P = 0.	47)						Favours PN Favours EN
Test for subgroup differenc	es: Chi = =	0.26, d	f=1 (P=	0.61),	l² = 0%			

Figure 7.2

		EN		PN		Risk Ratio			Risk Ratio		
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
	7.2.1 PEM										
	Holter et al 1977	24	26	28	30	0.8%	0.99 (0.85, 1.15)	1977			
	van Evs et al 1980	9	11	18	25	0.1%	1.14 [0.78, 1.65]	1980			
	Thompson et al 1981	9	9	12	12	0.5%		1981			
	Sako et al 1981	33	33	33	36	1 4 %		1981			
	Limetal 1981	10	12	11	12	0.2%	0.00 [0.07, 1.22]	1981			
	Donaldson et al 1982	12	13	11	12	0.2%		1987			
	Muller et al 1987	12	59	63	66	1 0%	0.85 (0.75, 0.97)	1002			
	Rickard at al 1983	07 A	8	10	10	0.3%		1002			
	Von Movenfeldt et al 1992	0 46	60	10	61	1 0%	0.06 [0.70, 1.27]	1002			
	Provide at al 1002	40	00	43	51	0.10%	0.30 [0.07, 1.00]	1002	•		
	Sound et al 1992	140	150	120	160	4.206		1002			
	Downoldo of ol 1007	140	100	130	100	4.2.70		1993			
	Reynolds et al 1997	31	33	33	34	1.0%	0.97 [0.87, 1.07]	1997			
	Hyltarider et al 2005	20	20	27	21	3.3%	1.00 [0.93, 1.07]	2005			
	Park et al 2012	18	18	20	20	1.7%	1.00 [0.91, 1.10]	2012			
	Klek et al 2014	82	84	82	83	10.2%	0.99 [0.95, 1.03]	2014	- -		
	Harvey et al 2016	48	80	36	55	0.2%	1.10 [0.83, 1.46]	2016			
	Subtotal (95% CI)		010		640	27.0%	0.99 [0.97, 1.02]		•		
	Total events	547		577							
	Heterogeneity: Tau ² = 0.00; ·	Chi ² = 10.	79, df :	= 15 (P =	0.77);1	²=0%					
	Test for overall effect: Z = 0.6	66 (P = 0.9	51)								
	7.2.2 No PEM										
	Ghavimi et al 1982	10	14	8	11	0.1%	0.98 [0.60, 1.60]	1982			
	Hays et al 1983	5	5	5	5	0.1%	1.00 [0.71, 1.41]	1983			
	Hamaoui et al 1990	10	11	8	8	0.2%	0.93 [0.71, 1.21]	1990			
	lovinelli et al 1993	24	24	24	24	2.7%	1.00 [0.92, 1.08]	1993			
	Brennan et al 1994	56	57	56	60	3.0%	1.05 [0.98, 1.14]	1994	+		
	Sand et al 1997	13	13	15	16	0.5%	1.06 [0.88, 1.26]	1997			
	Shirabe et al 1997	13	13	13	13	0.8%	1.00 [0.87, 1.15]	1997			
	Pacelli et al 2001	112	119	119	122	6.1%	0.96 [0.92, 1.02]	2001			
	Aiko et al 2003	20	20	19	19	1.8%	1.00 [0.91, 1.10]	2003			
	Jiang et al 2003	20	20	20	20	1.9%	1.00 [0.91, 1.10]	2003			
	Kamei et al 2005	27	27	21	21	2.6%	1.00 [0.92, 1.08]	2005			
	Liu et al 2011	28	28	30	30	3.9%	1.00 (0.94, 1.07)	2011			
	Li et al 2012	23	23	20	20	2.2%	1.00 (0.92, 1.09)	2012			
	Fuiita et al 2012	74	76	86	88	7.2%	1.00 (0.95, 1.05)	2012			
	Boelens et al 2014	61	61	62	62	17.3%	1.00 (0.97, 1.03)	2014	-		
	Dmvtrijev et al 2014	60	60	52	52	14.1%	1.00 [0.97, 1.04]	2014	_		
	Perinel et al 2016	96	103	99	101	4.9%		2016	_ -		
	Chen et al 2017	31	31	36	37	2.8%		2017	_ _		
	Subtotal (95% Cl)	51	705	50	709	72.4%	1.00 [0.98, 1.01]	2011	•		
	Total events	693		603					1		
$ \begin{array}{cccc} 0.00 & 0.00 $											
Text for verall effect 7 = 0.48 (P = 0.65)											
	Total (95% CI)		1321		1349	100.0 %	1.00 [0.98, 1.01]		•		
	Total events	1230		1270							
	Heterogeneity: Tau ² = 0.00; •	Chi ² = 18.	35, df =	= 33 (P =	0.98); I	²=0%					
	Test for overall effect: Z = 0.7	73 (P = 0	46)						Eavours PN Eavours EN		
	Test for subgroup difference	es: Chi = =	0.10, d	lf=1 (P=	0.75),	I ² = 0%					

Figure 7.3

	EN		PN		Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
7.3.1 Children									
van Evs et al 1980	9	11	18	25	0.1%	1.14 (0.78, 1.65)	1980		
Donaldson et al 1982	12	13	11	12	0.3%	1.01 [0.80, 1.27]	1982		
Ghavimi et al 1982	10	14		11	0.1%	0.98 (0.60, 1.60)	1982		
Havs et al 1983	5	5	5	5	0.1%		1983		
Dmytrijev et al 2014	60	60	52	52	14.1%		2014		
Subtotal (95% CI)	00	103	02	105	14.8%	1.00 [0.97, 1.04]	2014		
Total events	96		94						
Heterogeneity: Tau ^z = 0.00;	Chi ² = 1.1	1, df =	4 (P = 0.8	39); I * =	0%				
Heterogeneny: $ adr = 0.00, Chr = 1.11, dr = 4 (P = 0.89), r = 0\%$ Test for overall effect: Z = 0.07 (P = 0.95)									
7.3.2 Adults									
Holter et al 1977	24	26	28	30	0.8%	0.99 [0.85, 1.15]	1977		
Thompson et al 1981	9	9	12	12	0.5%	1.00 (0.84, 1.20)	1981		
Sako et al 1981	33	33	33	36	1.4%	1.09 [0.97, 1.22]	1981	<u> </u>	
Lim et al 1981	10	12	11	12	0.2%	0.91 [0.67, 1.23]	1981		
Muller et al 1982	48	59	63	66	1.0%	0.85 (0.75, 0.97)	1982		
Rickard et al 1983	6	6	10	10	0.3%		1983		
Hamaoui et al 1990	10	11	.0	.0	0.2%	0.93 [0.71, 1.21]	1990		
Smith et al 1992	5	6	6	6	0.2%	0.85 (0.55, 1.31)	1992		
Von Mevenfeldt et al 1997	46	50	л <u>а</u>	51	1.9%	0.00 [0.00, 1.01]	1002		
lovinelli et al 1993	24	24	74	24	2 7 96		1002		
Sandetrom et al 1993	140	150	120	160	1 206		1002	_	
Bronnon of al 1994	56	57	66	130	2.0%	1.05 [0.95, 1.00]	1004		
Downolde of al 1994	21	20	20	24	1 606	0.07 (0.30, 1.14)	1007		
Chirobo ot ol 1007	10	10	10	10	0.0%		1997		
Condict of 1007	10	10	15	10	0.0%	1.00 [0.07, 1.10]	1997		
Depailled at 1997	110	110	110	100	0.0%	0.06 (0.00, 1.20)	1997		
Fatelli et al 2001	20	20	119	122	0.170		2001		
Jiang et al 2003	20	20	20	20	1.970		2003		
Aiku et al 2003	20	20	19	19	1.8%		2003		
Hyltarider et al 2005	20	20	27	27	3.3%	1.00 [0.93, 1.07]	2005		
Kamereral 2005	27	27	21	21	2.0%	1.00 [0.92, 1.08]	2005		
	28	28	30	30	3.9%	1.00 [0.94, 1.07]	2011		
Lietaizuiz	23	23	20	20	2.2%	1.00 [0.92, 1.09]	2012		
Fujita et al 2012	14	/0	80	88	1.2%	1.00 [0.95, 1.05]	2012		
Park et al 2012	18	18	20	20	1.7%	1.00 [0.91, 1.10]	2012		
Kiek et al 2014	82	84	82	83	10.2%	0.99 [0.95, 1.03]	2014	1	
Boelens et al 2014	61	61	62	62	17.3%	1.00 [0.97, 1.03]	2014		
Perinei et al 2016	96	103	99	101	4.9%	0.95 [0.90, 1.01]	2016		
Harvey et al 2016	48	80	36	66	0.2%	1.10 [0.83, 1.46]	2016		
Chen et al 2017	31	31	36	37	2.8%	1.02 [0.95, 1.11]	2017		
Subtotal (95% CI)		1218		1244	85.2%	0.99 [0.98, 1.01]		•	
Total events	1134		1176						
Heterogeneity: Taur = 0.00;	Cni * = 17.	.83, df=	= 28 (P =	0.93);1	*=U%				
Lest for overall effect: $Z = 0.82$ (P = 0.41)									
Tetel (05% CI)		4224		4240	100.0%	4 00 10 00 4 041			
TO(81 (95% CI)		1521	1070	1549	100.0%	1.00 [0.98, 1.01]		1	
10tar events 1230 1270									
The terrogenerity, rate = 0.00; Chr = 18.35, dt = 33 (P = 0.98); r = 0% 0.7 0.85 1 1.2 1.5									
Test for overall effect: Z = 0.73 (P = 0.46) 0.7 0.85 1 1.2 1.5 Favours PN Favours EN							Favours PN Favours EN		
Test for subgroup differences: Chi ² = 0.14 df = 1 (P = 0.71) l ² = 0%									

Figure 7. No mortality for enteral nutrition (EN) and parenteral nutrition (PN) patients **7.1** Analyses by EN – tube feeding and standard care **7.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **7.3** Analyses by age of population – children and adults

<u>Study name</u>		C <u>um</u>	ulative s	tatistics	Cum	Cumulative mh		
	Point	Lower limit	Upper limit	Z-Value	p-Value	risk rat	9 (95% CI)	
Holter et al 1977	0.989	0.854	1.145	-0.148	0.882	· ·	- I	
van Eys et al 1980	1.008	0.879	1.155	0.111	0.912		_	
Sako et al 1981	1.055	0.968	1.150	1.214	0.225		+	
Lim et al 1981	1.043	0.960	1.134	1.001	0.317		- +-	
Muller et al 1982	0.986	0.919	1.058	-0.400	0.689		-	
Ghavimi et al 1982	0.986	0.919	1.057	-0.406	0.684		-	
Donaldson et al 1982	0.987	0.924	1.056	-0.372	0.710		+	
Hamaoui et al 1990	0.984	0.922	1.050	-0.498	0.619			
Von Meyenfeldt et al	19920.976	0.924	1.030	-0.889	0.374			
Smith et al 1992	0.974	0.923	1.027	-0.974	0.330			
Sandstrom et al 1993	0.990	0.951	1.032	-0.458	0.647		+	
Brennan et al 1994	1.004	0.969	1.041	0.226	0.821		+	
Sand et al 1997	1.006	0.971	1.043	0.343	0.731		+	
Reynolds et al 1997	1.002	0.969	1.036	0.128	0.898		+	
Pacelli et al 2001	0.991	0.964	1.020	-0.598	0.550		4	
Fujita et al 2012	0.993	0.969	1.017	-0.591	0.554		4	
Klek et al 2014	0.991	0.971	1.013	-0.801	0.423		4	
Harvey et al 2016	0.992	0.971	1.013	-0.750	0.453		4	
Perinel et al 2016	0.987	0.967	1.007	-1.270	0.204		4	
Chen et al 2017	0.989	0.970	1.009	-1.074	0.283		4	
	0.989	0.970	1.009	-1.074	0.283		•	
						0.5	1	
						Favours PN	Favours EN	

Figure 8. No mortality for enteral (EN) and parenteral nutrition (PN) patients, over time

2

Appendix 1. Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 20, 2018> Search Strategy:

- _____
- 1 exp Parenteral Nutrition/ (23169)
- 2 exp Enteral Nutrition/ (18501)
- 3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (31068)
- 4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (26309)
- 5 (1 or 3) and (2 or 4) (6209)
- 6 exp Comparative Study/ (1815838)

7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (6846615)

8 or/6-7 (6846615)

- 9 5 and 8 (2502)
- 10 limit 9 to english language (2120)
- 11 limit 10 to randomized controlled trial (288)

Database: Embase Classic+Embase <1947 to 2018 Week 51> Search Strategy:

- 1 exp parenteral nutrition/ (47926)
- 2 exp enteric feeding/ (29141)
- 3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (49280)
- 4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (41156)
- 5 (1 or 3) and (2 or 4) (10801)
- 6 exp comparative study/ (1327146)
- 7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (9108614)
- 8 or/6-7 (9108614)
- 9 5 and 8 (4130)
- 10 limit 9 to english language (3499)
- 11 limit 10 to randomized controlled trial (402)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2018> Search Strategy:

- 1 exp Parenteral Nutrition/ (1554)
- 2 exp Enteral Nutrition/ (1644)
- 3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (4161)
- 4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (4659)
- 5 (1 or 3) and (2 or 4) (1653)
- 6 exp Comparative Study/ (11)

7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (732365)

8 or/6-7 (732365)

9 5 and 8 (826)

10 limit 9 to english language (545)









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Appendix 4. Assessment of publication bias for endpoint "No infection" **4.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **4.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **4.3** Assessment by age of population – children and adults

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Appendix 5. Assessment of publication bias for endpoint "No nutrition support complications" 5.1 Assessment by enteral nutrition (EN) – tube feeding and standard care 5.2 Assessment by nutrition status – protein energy malnutrition (PEM) and PEM 5.3 Assessment by age of population – children and adults



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Appendix 6. Assessment of publication bias for endpoint "No major complications" 6.1 Assessment by enteral nutrition (EN) – tube feeding and standard care 6.2 Assessment by nutrition status – protein energy malnutrition (PEM) and PEM 6.3 Assessment by age of population – children and adults





Appendix 7. Assessment of publication bias for endpoint "No mortality" **7.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **7.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **7.3** Assessment by age of population – children and adults

This is a post-peer-review, pre-copyedit version of an article published in Supportive Care in Cancer. The final authenticated version is available online at: <u>https://doi.org/10.1007/s00520-019-05145-w</u>