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Network Meta-Analysis of Perioperative Nutrition

PROJECT TITLE: Does perioperative nutrition improve clinical outcomes in patients undergoing upper gastrointestinal surgery?: A network meta-analysis

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SUMMARY:

Each year in Canada, more than 2000 patients undergo surgical resection for treatment of esophageal, pancreatic, or stomach cancer. However, resection of upper gastrointestinal malignancies is associated with significant mortality and morbidity. One reason for the high rate of complications in this population of patients is preoperative malnutrition. To counteract the effects of malnutrition, post-operative nutritional support is often provided to these patients. Nutrition can be provided directly into the central circulation by total parenteral nutrition (TPN) or into the GI tract via a nasojejunal tube (a catheter passed through the nose into the small bowel) or a surgically placed jejunostomy tube (through the anterior abdominal wall and into the small bowel). It remains unclear which method of nutrient delivery, if any, provides the best overall patient outcomes. For this reason we have undertaken a network meta-analysis to evaluate the effects of the various perioperative nutritional delivery methods on clinical outcomes in patients undergoing upper gastrointestinal surgery.

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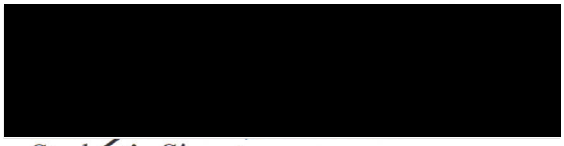

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Introduction:

Each year in Canada, more than 2000 patients undergo surgical resection for treatment of esophageal, pancreatic or stomach cancer (1, 2). However, resection of upper gastrointestinal (GI) malignancies is associated with significant mortality and morbidity. Recent cohort studies have estimated the rates of mortality and morbidity associated with esophageal resection to be 9.8% and 49.5%, respectively (3). Gastrectomies had rates of 7.6% and 33.3% (4), while pancreatectomies had rates of 3.8% and 33.8% (5).

One reason for the high rate of complications in this population of patients is preoperative malnutrition. Significant weight loss of greater than 10% is seen in 20-30% of patients undergoing resection of upper GI malignancies (4-6). This situation is made worse by the starvation that occurs in the postoperative period, since patients typically remain without oral intake for 7 days after surgery to allow for the anastomosis to heal and the integrity of the GI tract to be re-established.

To counteract the effects of malnutrition, post-operative nutritional support is often provided to these patients. Nutrition can be provided directly into the central circulation by total parenteral nutrition (TPN) or into the GI tract via a nasojejunal tube (a catheter passed through the nose into the small bowel) or a surgically placed jejunostomy tube (through the anterior abdominal wall and into the small bowel). Enteral nutritional compounds are available as either “standard” formulation or “immune enhanced” formulation.

Although there is evidence that nutritional support improves laboratory markers of immune function (7, 8), it remains unclear if this results in meaningful improvements in clinical outcomes (9, 10).

In a literature review of critically ill patients McCave and Heyland found that enteral nutrition enhances immune function and results in improved outcomes. However, this effect is not as evident with parenteral nutrition (8). As their study only includes critically ill patients with a variety of disease states, it is questionable if their findings remain valid for patients undergoing elective operations.

Although it is unclear whether nutritional support provides a clinical benefit, there are clear risks associated with providing nutrition. TPN and enteral nutrition both have complications that can range from troublesome to life threatening (11-18).

Most studies that have addressed the issue of perioperative nutrition have assumed that nutritional support is beneficial and compared one form of intervention to another. There have been few studies of sufficient size to answer the most fundamental question: Does perioperative nutritional support of any kind lead to improved clinical outcomes?

There are many options for providing nutritional support. In a primary review of the literature we were able to identify seven types of interventions: 1) fluid hydration alone, 2) standard enteral formulation delivered via nasojejunal tubes, 3) standard enteral nutrition delivered via a jejunostomy tube, 4) enhanced enteral formulation delivered via a nasojejunal tube, 5) enhanced

enteral formulation delivered via a jejunostomy tube, 6) standard total parenteral nutrition, and 7) enhanced total parenteral nutrition. This leads to twenty-one possible two-armed comparisons, but previous meta-analyses have studied only a subset of the possible comparisons.

Previous studies have combined data from patients undergoing a variety of types of GI surgery, including colorectal, despite the fact that these patients have different risk profiles and outcomes that are likely to affect the conclusions. For example, Drolet found that in a study of 54,000 patients in the US, patients undergoing elective colorectal surgery presented with malnutrition rates of 4-6% and had a mortality rate of 3.1%, compared to 20-30% and 10% for those undergoing upper GI surgery (19).

Previous studies have also neglected to consider the route of nutritional delivery despite the likely differences in possible complications from each method.

For this study, we undertook a multiple-treatment comparison using a network meta-analysis in order to incorporate the entire evidence base on effectiveness of nutritional interventions. We limited the study to upper GI resections to maintain a consistent risk profile and took route of nutritional delivery into consideration.

Network meta-analysis is a relatively new statistical technique that allows for integration of direct (head-to-head) comparisons and control (i.e., fluid hydration alone) comparisons. It also permits inferences into the relative efficacy of treatments that may not have been compared to each other in direct randomized control trials. Network meta-analysis therefore provides a clinically useful synthesis that can help guide treatment decisions (20-27).

Objective

The primary objective of this study was to determine if patients undergoing surgical resection and reconstruction of the upper GI tract for carcinoma benefit from nutritional support provided in the first seven days after surgery.

Methods

We performed a systematic review and a network meta-analysis of randomized control trials. Studies were required to meet four inclusion criteria to be considered in the review: 1) reports on adult patients undergoing elective esophagectomy, gastrectomy, or pancreatectomy for resection of upper GI carcinoma, 2) is a randomized control trial, 3) compares at least two nutritional interventions that were delivered during the first seven days after surgery, and 4) reports at least one of our outcomes of interest.

Search strategy: A search strategy incorporating key terms and MeSH headings (see Appendix 1) was performed in June, 2011 across the following well-known databases: PubMed (MEDLINE); SCOPUS; Web of Knowledge; EMBASE; and the Cochrane Library. When possible, filters employed in search strategies across the various databases attempted to retrieve randomized controlled trials appearing in journals and conference proceedings. As noted in the appendix, the date ranges searched varied depending on database coverage.

Selection of studies: We merged the electronic search results using RefWorks, a reference management software suite, and removed duplicate reports. The search yielded 936 studies, for which two reviewers examined the titles and abstracts. A study was included for full-text review if either reviewer considered it relevant according to the inclusion and exclusion criteria. Two reviewers independently reviewed the 191 full texts of the retrieved articles for inclusion using the specified criteria, which resulted in 26 included studies (Figure 1). Disagreements were resolved by discussion or by a third independent reviewer.

Data extraction and management: After a final decision on inclusion, assessment of methodological quality (risk of bias) and data for the specified outcomes were extracted independently by two reviewers into a custom electronic database created using FileMaker Pro 11 (FileMaker Inc. Santa Clara, USA). Further information including details on study design, participants, interventions, and follow-up were also extracted. Authors were contacted if there was a need for additional information. Discrepancies were discussed until a consensus was reached and further unresolved issues were passed to a third reviewer.

Sources of bias: The risk of bias in the included studies was assessed and reported using the method outlined in the Cochrane Handbook Chapter 8, Section 8.5 (28). A summary of the risk of bias across studies was created using a risk of bias summary figure (Figure 2).

Assessment of heterogeneity: We found there to be too few studies in each possible pairwise comparison to determine sources of heterogeneity. Therefore we only report the I^2 as a measure of heterogeneity.

Data synthesis: We performed a standard fixed-effect meta-analysis to determine the odds ratios and 95% confidence intervals for each of five primary outcomes 1) 30-day mortality, 2) anastomotic failure, 3) sepsis, 4) pulmonary infections, and 5) total infections. A continuity correction was required for events that occurred zero times in various studies. This was accomplished by the addition of 0.5 to each value where there were zero events reported. Next, a fixed-effect network meta-analysis within a Bayesian framework was undertaken (Figure 3).

For all analyses we used no nutritional intervention, i.e. intravenous hydration only prior to oral intake, as the reference standard.

Sensitivity analysis: Sensitivity analysis was carried out to determine how the effect size estimates varied according to the method selected for dealing with zero events. We found that the estimate of the effect remained similar across these analyses regardless of the continuity correction method used (exclude studies with zero events, use of 0.5 for continuity corrections, and use of 0.01 for continuity corrections).

Results

There were 26 studies included in this review (29-54)(Table 1a). The raw agreement for inclusion was 91.6% and the Kappa was 0.76, which indicates excellent agreement for inclusion. There were 34 papers for which we are in the process of acquiring further information (require translation, or clarification by author).

The 26 studies reported on 2452 patients of whom 31% underwent esophagectomy, 38% underwent gastrectomy, and 25% underwent pancreatectomy (Table 1b). The mean age of the patients was 64.6 years. The median mortality rate reported across the studies was 2.30% with an interquartile range of 0.00% to 2.98%. The median and interquartile range for anastomotic failure, sepsis, pulmonary infection and total infections was 8.25% (4.43-13.33%), 4.55% (3.08-5.78%), 13.8% (7.7-22.4%), and 23.1% (17.5-39.6%) respectively (Table 2).

The trials ranged from 20-257 participants with the median number of participants being 68.5. There were two studies with more than 200 participants and nine having less than 50 participants (Table 1a).

Only 38% (10/26) of studies reported the number of patients who had significant weight loss prior to surgery. Of the 10 studies that did report this information, a median of 29.5% (range 17% to 54%) of patients had significant (>10%) weight loss (Table 1b).

Most studies were not blinded, given the nature of the interventions. However, 54% of the studies were at low risk of bias for adequate concealment of allocation and 62% were at low risk of bias for intention to treat analysis (Figure 2).

We combined standard and immune enhanced forms of nutrition delivery to increase the power of the analysis. To test the assumption that these were sufficiently similar to combine we performed a preliminary analysis where standard and enhanced nutrition were considered separately. We found very similar results between the two for all outcomes except total rate of infection, which appeared to favor enhanced (Table 3).

For the primary outcome of mortality, the network meta-analysis odds ratio estimates suggested that the use of either standard or enhanced nutrition delivered via jejunostomy was associated with an elevated risk of death (odds ratio of 1.44, 95% CI (0.34, 5.10)). The odds ratio estimates also suggested that enteral nutrition delivered by a nasojejunal tube and TPN lead to decreased mortality (odds ratios of 0.44 (0.10, 1.59) and 0.22 (0.04, 0.94), respectively). However, considerable uncertainty is associated with these estimates due to the limited number of deaths in the included trials. All interventions appeared to decrease the risk of anastomotic failure, albeit not significantly. The odds ratio estimates for nutrition delivered via jejunostomy suggested a more pronounced risk reduction than for the other interventions. For sepsis, the odds ratio estimates suggested a decreased risk with jejunostomy, but an increased risk with nasojejunal tube and TPN. However, considerable uncertainty surrounds these estimates due to a very limited number of events and trials informing this outcome. Jejunostomy, nasojejunal, and TPN all produced similar odds ratio estimates (and beneficial effects) for pulmonary infection (odds ratios of 0.33 (0.13, 0.74), 0.44 (0.15, 1.19), and 0.40 (0.13, 1.11), respectively). Lastly, jejunostomy and nasojejunal tube were associated with a decrease in total reported infections (odds ratios of 0.68 (0.44, 1.07) and 0.82 (0.43, 1.49), respectively), whereas TPN did not appear to reduce the proportion of total reported infections (1.04 (0.57, 1.89)) (Table 3)(Figure 4).

When we undertook direct comparisons, certain point estimates were somewhat inconsistent with those of the network meta-analyses. However, the wide confidence intervals and the potential for

Type-I errors due to multiple testing may explain these discrepancies. We therefore felt comfortable combining all trials in the network meta-analysis.

Discussion

Main results: We carried out a systematic review and a network meta-analysis of randomized control trials to determine the effect of perioperative nutritional support in patients undergoing resection and reconstruction of upper gastrointestinal cancer.

We found 26 studies including 2452 patients. The studies were generally small and often did not report the degree of weight loss in their study populations. The number of events reported in the studies was small, and a large number reported no events for some of their outcomes, reflecting the relatively low overall event rate.

The overall trend is that perioperative nutritional support is associated with a decreased risk of anastomotic failure, sepsis, pulmonary infections and total infections when compared to no nutritional support. For these outcomes there does not appear to be any significant differences between enteral nutrition, delivered by nasojejunal tube or surgical jejunostomy, and TPN. However, there is a suggestion that mortality is elevated when a surgical jejunostomy tube is used. In Canada, the primary method for providing nutrition to this patient population is the jejunostomy tube, which makes the suggestion of increased mortality particularly concerning. The potentially significant complications attributable to this means of nutritional delivery have been suggested in the past (55, 56).

The potential benefits ascribed to perioperative nutritional support may well be true given our findings, but the width of the confidence intervals around our estimates brings into question the strength of this evidence. We expected to find more robust evidence for the benefit of perioperative nutrition as we limited our study to patients at relatively high risk of adverse events and thus were more likely to benefit from an intervention if it were effective. Instead, we found that the benefits of perioperative nutrition methods were not convincing, despite their wide use. These findings are similar to that reported in previous meta-analyses by Lewis and Mazaki (9, 18).

Clearly, there are a large number of factors that would account for the wide confidence intervals and uncertainty of effect. There is likely to be clinical heterogeneity and differing outcome definitions across the included studies even with the small values for I^2 seen in the analysis.

The variation in the proportion of patients with >10% weight loss is one likely reason for heterogeneity. Significant weight loss is a strong a predictor of morbidity and mortality after upper GI surgery (4, 57). Due to the small number of studies in each of the comparisons and the number of studies where this information was actually available (10/26 studies), we were unable to undertake a formal subgroup analysis based on this factor. However, the variation in the proportion of patients with significant weight loss (17-54%) is noticeable (Table 1b).

We noted that there were some inconsistencies between the estimates given by the standard meta-analysis and the network meta-analysis. This could be accounted for by the wide confidence intervals around the estimates from both methods. Another reason for the differential estimates is that by design, the network meta-analysis gains information from the indirect comparisons that is likely to alter the estimates. Since a major reason for undertaking a network meta-analysis was the expectation that the pairwise comparisons were likely to be few, the extra information from the indirect comparisons is beneficial.

Strengths of this study: As far as we are aware, this is the only systematic review that specifically addresses the question of perioperative nutritional support in patients undergoing upper gastrointestinal surgery. Patients with upper GI malignancies are more likely to be malnourished, as they undergo a generally more significant surgical insult and experience a longer period of limited oral intake. All of these factors should lead to a higher event rate and if an intervention is effective it should be more apparent in this population. Previous systematic reviews have included patients undergoing other types of gastrointestinal surgery that generally have a lower risk of the major outcomes that we were concerned with.

Using network meta-analysis we were able to include all interventions and comparisons, which has not been done previously. This strategy also deals with a potential source of bias in systematic reviews and meta-analysis where the conclusions are drawn from only a certain subset of possible comparisons.

Previous meta-analyses have not taken into consideration the route of nutritional delivery. Given the different risk profiles of the three routes of delivery, we feel that this is an important consideration.

Limitation of this study: Like all systematic reviews, this is ultimately an observational study and is therefore subject to inherent bias. We took care to undertake a wide search and did not exclude on the basis of language. However, due to time constraints, there are a number of studies which may be eligible for inclusion but for which do not have sufficient information at this time.

Conclusions

This study demonstrated that the evidence for the routine use of perioperative nutritional support in patients undergoing upper GI surgery is suggestive but weak. The effect size is credible, but the confidence intervals are wide. The increased risk of mortality in patients receiving nutritional support through a jejunostomy is concerning.

It seems that the role of perioperative nutrition in the setting of upper GI surgery is not settled. There are no trials of sufficient size or of adequate design to address this question and further small studies are unlikely to change the situation. This is the third systematic review that has tried to address this issue and the third study that has come to a similarly tentative conclusion.

A large and well-designed randomized trial is required to clarify the situation. The trial should compare the effect of enteral nutrition delivered by a nasojejunal tube, enteral nutrition delivered

by jejunostomy, and no early nutrition. The study should also be of sufficient size to allow for stratification based on the degree of weight loss.

Given the significant number of patients who undergo upper GI surgery for carcinoma each year in Canada, determining an optimal nutritional management strategy is critical.

Appendix 1: Database Search Strategies and Date Coverage

PubMed (MEDLINE) Search – 1949- June 2011
MeSH Terms: enteral nutition, jejunostomy, nutritional sciences, "surgical procedures, operative", general surgery, reconstructive surgical procedures, esophagus, esophageal diseases, stomach, neoplasms, carcinoma

Search Terms: enteral nutrition, enteral feeding, perioperative, jejunostomy, nasojejunal, nutritional sciences, nutritional management, nutritional support, surgery, surgical procedures, general surgery, resection, reconstructive surgical procedures, reconstruction, esophagus, esophageal diseases, stomach, upper gastrointestinal, neoplasms, cancer, carcinoma

Limits: Humans Type of Article: Clinical Trial, Meta-analysis, Practice guideline, Randomized control trial, review, comparative study

EMBASE (OvidSP) – 1974 – June 2011
#1 (neoplasm* or cancer* or carcinoma* or adenocarcinoma*)
#2 (esophagus or esophageal or "upper gastrointestinal" or stomach or oesophagus or oesophageal)
#3 (surger* or "surgical procedures" or "surgical procedure" or reconstruct* or resect*)
#4 ("enteral nutrition" or "enteral feeding" or "jejunostomy feeding" or "jejunostomy tube" or "jejunostomy tubes" or "nasojejunal feeding" or "nasojejunal tube" or "nasojeujunal tubes" or "nutritional support" or "nutritional management" or "perioperative nutrition" or "nutritional sciences")

Title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, and drug manufacturer names were searched

Web of Knowledge (Thomson Reuters) 1864- June 2011
#1 TS=("enteral nutrition" or "enteral feeding" or "jejunostomy feeding" or "jejunostomy tube" or "jejunostomy tubes" or "nasojejunal feeding" or "nasojejunal tube" or "nasojeujunal tubes" or "nutritional support" or "nutritional management" or "perioperative nutrition" or "nutritional sciences")
#2 TS=(surger* or "surgical procedures" or "surgical procedure" or reconstruct* or resect*)
#3 TS=(esophagus or esophageal or "upper gastrointestinal" or stomach or oesophagus or oesophageal)
#4 TS=(neoplasm* or cancer* or carcinoma* or adenocarcinoma*)

Cochrane Library (John Wiley and Sons)
#1 (neoplasm* or cancer* or carcinoma* or adenocarcinoma*) Search All Text
#2 (esophagus or esophageal or "upper gastrointestinal" or stomach or oesophagus or oesophageal) Search All Text
#3 (surger* or "surgical procedures" or "surgical procedure" or reconstruct* or resect*) Search All Text

#4 ("enteral nutrition" or "enteral feeding" or "jejunostomy feeding" or "jejunostomy tube" or "jejunostomy tubes" or "nasojejunal feeding" or "nasojejunal tube" or "nasojeujunal tubes" or "nutritional support" or "nutritional management" or "perioperative nutrition" or "nutritional sciences") Search All Text

SCOPUS (Elsevier) - 2004 – June 2011
#1 TITLE-AB-Key(neoplasm* or cancer* or carcinoma* or adenocarcinoma*)
#2 TITLE-AB-Key(esophagus or esophageal or "upper gastrointestinal" or stomach or oesophagus or oesophageal)
#3 TITLE-AB-Key(surger* or "surgical procedures" or "surgical procedure" or reconstruct* or resect*)
#4 TITLE-AB-Key("enteral nutrition" or "enteral feeding" or "jejunostomy feeding" or "jejunostomy tube" or "jejunostomy tubes" or "nasojejunal feeding" or "nasojejunal tube" or "nasojeujunal tubes" or "nutritional support" or "nutritional management" or "perioperative nutrition" or "nutritional sciences")

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Table 1a: Study Characteristics

Author	Year	Ref #	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Subjects
Barlow	2011	33	Nil	SEN-J			121
Hyltander	2005	29	Nil	SEN-J	S-TPN		80
Heslin	1997	41	Nil	EEN-J			195
Page	2002	48	Nil	SEN-NJ			40
Cooper	2006	36	Nil	S-TPN			34
Kamei	2005	44	Nil	S-TPN			52
Wu	1995	54	Nil	S-TPN			51
Daly	1992	37	SEN-J	EEN-J			85
Farreras	2005	38	SEN-J	EEN-J			66
Giger	2007	39	SEN-J	EEN-J			46
Kenler	1996	32	SEN-J	EEN-J			50
Lobo	2006	47	SEN-J	EEN-J			120
Ryan	2009	31	SEN-J	EEN-J			70
Sakurai	2007	49	SEN-J	EEN-J			30
Senkal	1997	52	SEN-J	EEN-J			164
Senkal	1999	53	SEN-J	EEN-J			178
Han-Geurts	2007	40	SEN-J	SEN-NJ			150
Aiko	2003	30	SEN-J	S-TPN			39
Heylen	1987	42	SEN-J	S-TPN			20
Reynolds	1997	43	SEN-J	S-TPN			67
Klek	2008	45	SEN-NJ	EEN-NJ			196
Klek	2008	46	SEN-NJ	EEN-NJ	S-TPN	E-TPN	205
Sand	1997	50	SEN-NJ	S-TPN			29
Seike	2011	51	SEN-NJ	S-TPN			30
Braga	1995	35	SEN-NS	EEN-NS	S-TPN		77
Braga	2001	34	SEN-NS	S-TPN			257

Note: Nil = No Early Nutrition, SEN-J = Standard Enteral Nutrition – Jejunostomy, EEN-J = Enhanced Enteral Nutrition – Jejunostomy, SEN-NJ = Standard Enteral Nutrition – Nasojejunal, EEN-NJ = Enhanced Enteral Nutrition – Nasojejunal, SEN-NS = Standard Enteral Nutrition - Non-Specified, EEN-NS = Enhanced Enteral Nutrition - Non-Specified, S-TPN = Standard TPN, E-TPN = Enhanced TPN

Table 1b: Patient Characteristics

Author	Year	Ref #	Subjects	Mean age	% Male	% Esophageal Surgery	% Gastric Surgery	% Pancreatic Surgery	% with > 10% Weight Loss
Barlow	2011	33	121	NR	68.6	45	31	24	NR
Hyltander	2005	29	80	62.3	65.8	38	22	40	43
Heslin	1997	41	195	NR	60.0	14	37	49	NR
Page	2002	48	40	67.4	70.0	100	0	0	NR
Cooper	2006	36	34	68	81.5	100	0	0	NR
Kamei	2005	44	52	63.5	71.2	0	100	0	NR
Wu	1995	54	51	72.5	92.5	0	100	0	NR
Daly	1992	37	85	62.5	63.5	35	25	21	32
Farreras	2005	38	66	68	53.3	0	100	0	22
Giger	2007	39	46	61	58.7	0	26	74	54
Kenler	1996	32	50	63.6	74.3	37	6	37	NR
Lobo	2006	47	120	66	76.9	59	27	14	NR
Ryan	2009	31	70	63.9	88.4	100	0	0	18
Sakurai	2007	49	30	63	43.3	100	0	0	NR
Senkal	1997	52	164	65.7	NR	19	51	20	NR
Senkal	1999	53	178	65.5	64.9	17	38	13	NR
Han-Geurts	2007	40	150	NR	80.0	100	0	0	NR
Aiko	2003	30	39	65	84.6	100	0	0	NR
Heylen	1987	42	20	NR	NR	0	100	0	NR
Reynolds	1997	43	67	68	79.1	63	21	16	27
Klek	2008	45	196	62.2	62.3	0	62	38	19
Klek	2008	46	205	61.2	70.9	0	62	38	17
Sand	1997	50	29	NR	37.9	0	100	0	NR
Seike	2011	51	30	63.7	90.0	100	0	0	NR
Braga	1995	35	77	60.2	54.3	0	56	44	53
Braga	2001	34	257	63.5	54.1	10	47	43	35

Note: NR = Not Reported

Table 2: Overall Rate of Outcomes

Author	Year	Ref #	Patients	Mortality (%)	Anastomotic Failure (%)	Sepsis (%)	Pulmonary Infection (%)	Total Rate of Infection (%)
Barlow	2011	33	121	2.5	7.4	NR	14.0	40.5
Hyltander	2005	29	80	NR	NR	8.8	NR	18.8
Heslin	1997	41	195	2.6	7.2	1.0	5.1	22.1
Page	2002	48	40	0.0	NR	NR	NR	2.5
Cooper	2006	36	34	7.4	NR	3.7	NR	3.7
Kamei	2005	44	52	0.0	6.3	NR	NR	6.3
Wu	1995	54	51	0.0	12.5	NR	0.0	2.5
Daly	1992	37	85	2.4	NR	NR	NR	21.2
Farreras	2005	38	66	5.0	NR	0.0	3.3	18.3
Giger	2007	39	46	2.2	NR	NR	NR	37.0
Kenler	1996	32	50	2.9	NR	5.7	11.4	57.1
Lobo	2006	47	120	NR	16.7	5.6	34.3	51.9
Ryan	2009	31	70	0.0	3.8	13.2	22.6	39.6
Sakurai	2007	49	30	NR	16.7	NR	16.7	30.0
Senkal	1997	52	164	3.2	11.0	3.9	11.0	22.7
Senkal	1999	53	178	NR	7.8	5.2	8.4	17.5
Han-Geurts	2007	40	150	5.3	8.7	NR	37.3	55.3
Aiko	2003	30	39	0.0	0.0	NR	7.7	23.1
Heylen	1987	42	20	NR	0.0	NR	NR	15.0
Reynolds	1997	43	67	4.5	3.0	6.0	22.4	49.3
Klek	2008	45	196	1.1	3.8	NR	15.3	24.0
Klek	2008	46	205	2.0	13.7	3.9	23.9	52.2
Sand	1997	50	29	0.0	10.3	NR	13.8	27.6
Seike	2011	51	30	NR	43.3	NR	NR	NR
Braga	1995	35	77	0.0	NR	NR	NR	13.0
Braga	2001	34	257	2.7	13.6	1.2	3.5	24.5

Note: NR = Not Reported

Table 3: Direct and Indirect Comparisons

Outcome	Comparison	Data Ref #	# of Studies	OR	95% CI	I^2 (%)		Network OR	Network 95% CI
Mortality	Nil vs EN-J	1A	2	1.52	(0.39, 5.88)	41.7		1.44	(0.34, 5.10)
	Nil vs EN-NJ	1B	1	1.00	(0.02, 50.0)			0.44	(0.10, 1.59)
	Nil vs TPN	1C	3	0.36	(0.05, 2.44)	0		0.22	(0.04, 0.94)
	EN-J vs TPN	1D	2	0.58	(0.07, 4.55)	0		0.13	(0.02, 0.57)
	EN-NJ vs TPN	1E	2	1.00	(0.17, 5.88)	0		0.54	(0.14, 1.69)
	EN Stand vs EN Enh	1F	9	1.05	(0.44, 2.50)	0			
Anastomotic failure	Nil vs EN-J	2A	2	0.49	(0.20, 1.19)	27.8		0.43	(0.15, 1.14)
	Nil vs EN-NJ	2B	0					0.75	(0.29, 1.97)
	Nil vs TPN	2C	2	1.11	(0.26, 4.76)	0		0.67	(0.30, 1.46
	EN-J vs TPN	2D	3	1.00	(0.14, 7.14)	0		1.57	(0.63, 3.90)
	EN-NJ vs TPN	2E	3	0.91	(0.47, 1.79)	0		0.88	(0.47, 1.63)
	EN Stand vs EN Enh	2F	7	0.78	(0.48, 1.25)	0			
Sepsis	Nil vs EN-J	3A	2	1.02	(0.10, 10.0)	0		0.31	(0.05, 1.68)
	Nil vs EN-NJ	3B	0					3.39	(0.51, 22.6)
	Nil vs TPN	3C	2	3.70	(0.82, 16.7)	76.1		1.99	(0.62, 5.52)
	EN-J vs TPN	3D	2	7.69	(1.39, 50.0)	0		6.38	(1.48, 25.1)
	EN-NJ vs TPN	3E	1	0.62	(0.14, 2.63)			0.59	(0.11, 2.59)
	EN Stand vs EN Enh	3F	7	0.98	(0.49, 1.92)	0			
Pulmonary Infection	Nil vs EN-J	4A	2	0.35	(0.15, 0.84)	0		0.33	(0.13, 0.74)
	Nil vs EN-NJ	4B	0					0.44	(0.15, 1.19)
	Nil vs TPN	4C	1	1.00	(0.02, 50.0)			0.40	(0.13, 1.11)
	EN-J vs TPN	4D	2	1.30	(0.46, 3.57)	0		1.21	(0.62, 2.37)
	EN-NJ vs TPN	4E	2	0.89	(0.49, 1.67)	0		0.90	(0.52, 1.55)
	EN Stand vs EN Enh	4F	9	0.92	(0.64, 1.32)	0			
Total Infection	Nil vs EN-J	5A	3	0.56	(0.35, 0.91)	82.1		0.68	(0.44, 1.07)
	Nil vs EN-NJ	5B	1	3.13	(0.12, 100)			0.82	(0.43, 1.49)
	Nil vs TPN	5C	4	2.86	(1.05, 7.69)	51		1.04	(0.57, 1.89)
	EN-J vs TPN	5D	4	2.63	(1.35, 5.26)	50.4		1.54	(0.94, 2.52)
	EN-NJ vs TPN	5E	2	0.83	(0.50, 1.41)	0		1.29	(0.83, 2.04)
	EN Stand vs EN Enh	5F	12	0.67	(0.51, 0.88)	24.3			

Figure 1: Quorum Diagram

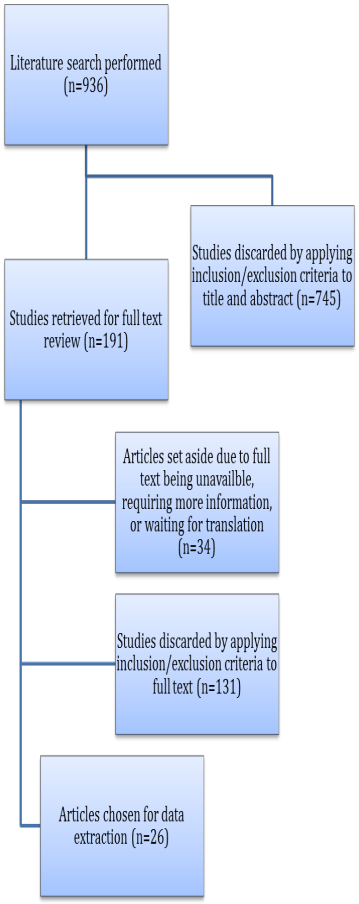
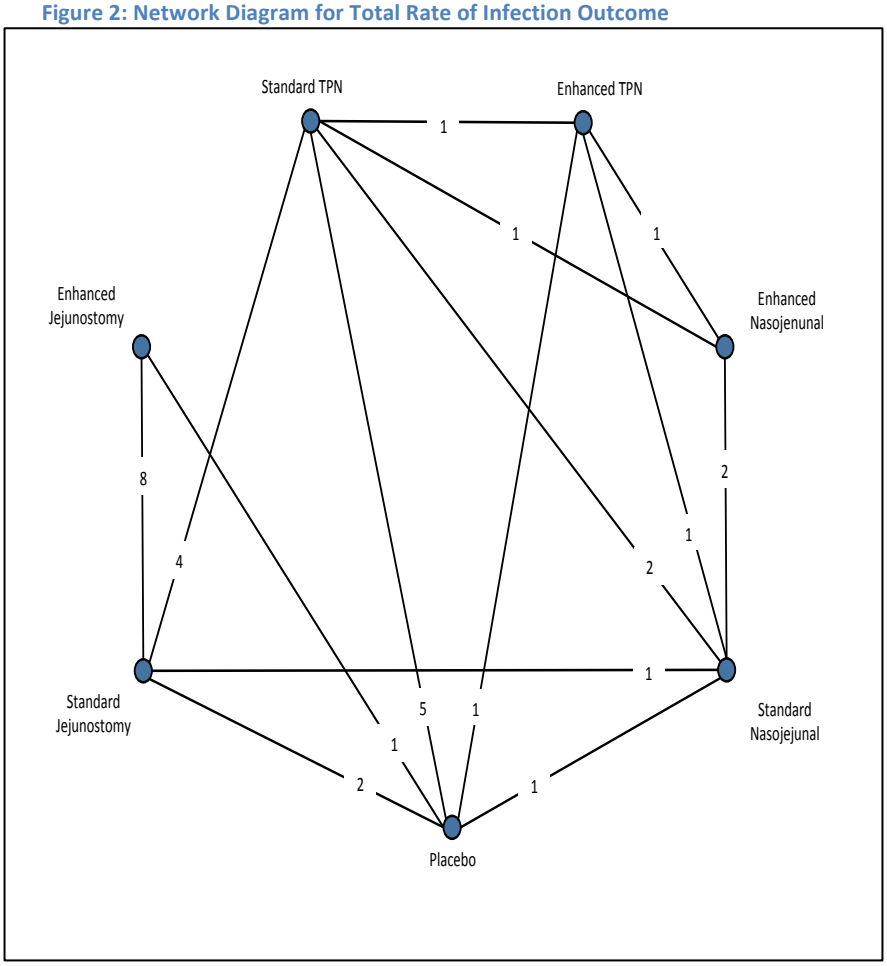


Figure 2: Network Diagram for Total Rate of Infection Outcome



Note: Numbers represent the number of studies that made each comparison

Figure 3: Risk of Bias Diagram

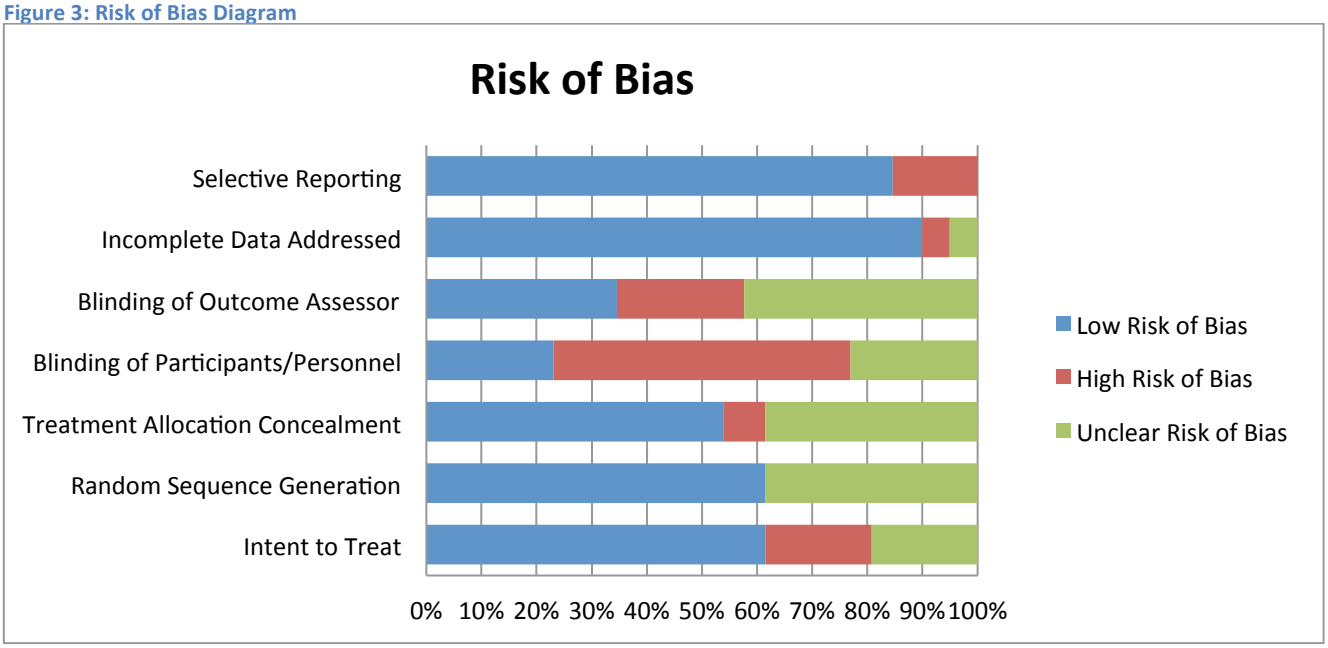


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Figure 4: Plots of Meta-Analysis Odds Ratios for Each Outcome