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REVIEW

What is the evidence for the use of parenteral nutrition (PN) in critically ill surgical patients: a systematic review and meta-analysis

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Abstract

Background Malnutrition is associated with poor outcomes in surgical patients and corrective enteral feeding may not be possible. This is a particular problem in the acute setting where malnutrition is prevalent. The aim of this systematic review was to evaluate the use of parenteral nutrition (PN) in critically ill surgical patients.

Methods This review was registered with PROSPERO (CRD42017079567). Searches of the CENTRAL, EMBASE, and MEDLINE databases were performed using a predefined strategy. Randomised trials published in English since 1995, reporting a comparison of PN vs any comparator in a critically ill surgical population were included. The primary outcome was mortality. Risk of bias was assessed using the Cochrane risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation assessment. Meta-analysis was performed using a random effects model to assess variation in mortality and length of stay.

Results Fourteen RCTs were identified; standard PN was compared vs other forms of PN in ten studies, to PN with variable dose amino acids in one, and to enteral nutrition (EN) in three. In trials comparing glutamine-supplemented PN (PN-GLN) to PN, a non-significant reduction in mortality was noted (risk difference −0.08. 95% CI −0.17, 0.01, $p = 0.08$). A trend for a reduction in length of stay was seen in PN-GLN to PN comparator (mean reduction −2.4, 95% CI −7.19 to 2.32 days, $I^2 = 92\%$). Impact on other outcome measures varied in direction of effect.

Conclusions PN may offer benefit in critically ill surgical patients. The size and quality of studies lead to uncertainty around the estimates of clinical effect, meaning a robust trial is required.

Keywords Nutritional support · Surgery · Critical illness · Gastrointestinal failure · Review

Introduction

Malnutrition is a well-documented challenge in surgery as it is associated with delayed healing, higher rates of complications and prolonged length of hospital stay [1–3]. A high proportion of patients admitted under the care of gastrointestinal surgeons are at risk of malnutrition, and reaching appropriate caloric intake in the postoperative period is problematic [4]. Most general surgery patients have an element of gastrointestinal failure either due to their primary pathology or due to surgical intervention, and cannot absorb nutrition as needed [5, 6]. These patients may require support by other methods, which may include intravenous fluids or the use of parenteral nutrition (PN). Problems related to malnutrition and intestinal failure may be compounded further if the patient is admitted to hospital with an acute surgical pathology: the patient may have endured acute gastrointestinal dysfunction or

K. Ledgard and B. Mann are co-first authors and they contributed equally to the work.

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failure for a period of time prior to admission and be in nutritional deficit. Current guidance in advocates that PN is not typically be started until 5–7 days post-surgery unless the patient has high nutritional risk or is in a hypermetabolic state [7–9]. The same guidance acknowledges that it is based upon low-to-moderate quality evidence.

There is a significant body of literature on the use of PN in the critical care setting [10]. Unfortunately, this cannot be easily translated to the general surgical population as it includes a large number of patients with non-surgical diagnoses. This population is unlikely to have the same degree of gastrointestinal dysfunction (mechanical or otherwise) as the gastrointestinal surgical population. PN has been established in elective perioperative nutrition for 25 years [11]; however, recent work evaluating its use in acute surgical admissions has shown variation in practice [12]. One reason for this may be an incomplete evidence base.

The aim of this study was to conduct a systematic review and meta-analysis to evaluate the effect of PN in critically ill gastrointestinal surgery patients with respect to mortality, length of stay and other complications of care.

Materials and methods

Protocol and registration

This review was conducted in accordance with the COCHRANE handbook [13], and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. It was prospectively registered on the PROSPERO database (CRD42017079567).

Eligibility criteria

Eligible studies were randomised controlled trials (RCTs) published in English, after 1995. For inclusion, the studies had to report outcomes of critically ill surgical patients. The patient group was defined as those requiring intensive care admission following elective or emergency abdominal gastrointestinal surgery (e.g. laparotomy, colorectal resection). Studies were eligible where they compared any form of PN to another form of PN, PN with enteral nutrition (EN), EN alone, placebo, or no nutrition intervention.

Excluded studies were those in which patients had elective preoperative feeding, paediatric cases, conditions treated by surgeons which do not require surgical interventions (e.g. pancreatitis) or trials involving packaged interventions. Studies reporting trauma populations were excluded.

Outcomes

The primary outcome was mortality. Secondary outcomes were hospital length of stay (LOS), hospital acquired infections (HAIs), nitrogen balance and weight change.

Information sources

Searches were performed of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (all time), MEDLINE (Ovid SP) from 1946 to September 2017 and Embase (Ovid SP) from 1974 to September 2017, which used no limits and combined Boolean operators, free text terms and thesaurus terms, no language or date limitation was applied. The search strategies used are given in Appendix 1 in Supplementary material. Additional citations were identified through expert recommendations and hand-searching of citations.

Study selection

Search results were imported into a citation management program (Covidence.org) and duplicates removed. Two investigators independently screened articles for eligibility against predefined exclusion criteria at the title/abstract and full-text stage; conflicts were resolved by a discussion with a third investigator.

Data extraction

Data were extracted into predefined tables by two reviewers and compared, with disagreements resolved as above. The following items were recorded: author, year, study design, basic population demographics, intervention and control arms, primary outcomes, and secondary outcomes including LOS, weight change, mortality at 6 months, mortality within the hospital admission, HAIs, complications and nitrogen balance. Nitrogen balance is a method used to estimate protein balance. Critically ill patients are typically in a catabolic state and will have a negative nitrogen balance (i.e. protein intake is not adequate). A positive or neutral balance shows that needs are being met or exceeded [15].

Risk of bias of individual studies

The Cochrane Risk of Bias tool was used independently by two authors to assess bias of relevant studies [13].

Summary measures

The summary methods for results obtained varied, but included population means with standard errors, differences, ratios, binary results with confidence ratios and tests of significance.

Synthesis of results

Pre-planned meta-analysis using a random effects model was used to assess risk difference for mortality, and mean difference for length of stay with Revman v5.3 software (Cochrane Collaboration, Copenhagen).

Risk of bias across studies

Using the GRADE PRO tool, bias was assessed across the studies for the primary outcome of death, within all comparators [16].

Results

Study selection

The search identified 2638 references (Fig. 1). Following the removal of duplicates, 1636 papers, were screened for inclusion. Eighty-six papers were reviewed at full text, and 14 of them were included in the review. Seventy-two were rejected at this stage for the following reasons: no PN comparator ($n=28$), non-emergency population ($n=25$), article in not in the English language ($n=8$), no placebo comparator ($n=2$), ineligible comparator ($n=2$), ineligible intervention ($n=2$), ineligible patient population ($n=2$), ineligible study design ($n=2$), published before 1995 ($n=1$).

Study characteristics

The included studies included ten trials comparing standard PN against a supplemented PN [1, 17–25]; three trials comparing PN against EN [26–28], one of which also compared PN to no nutrition intervention [26] and one trial comparing

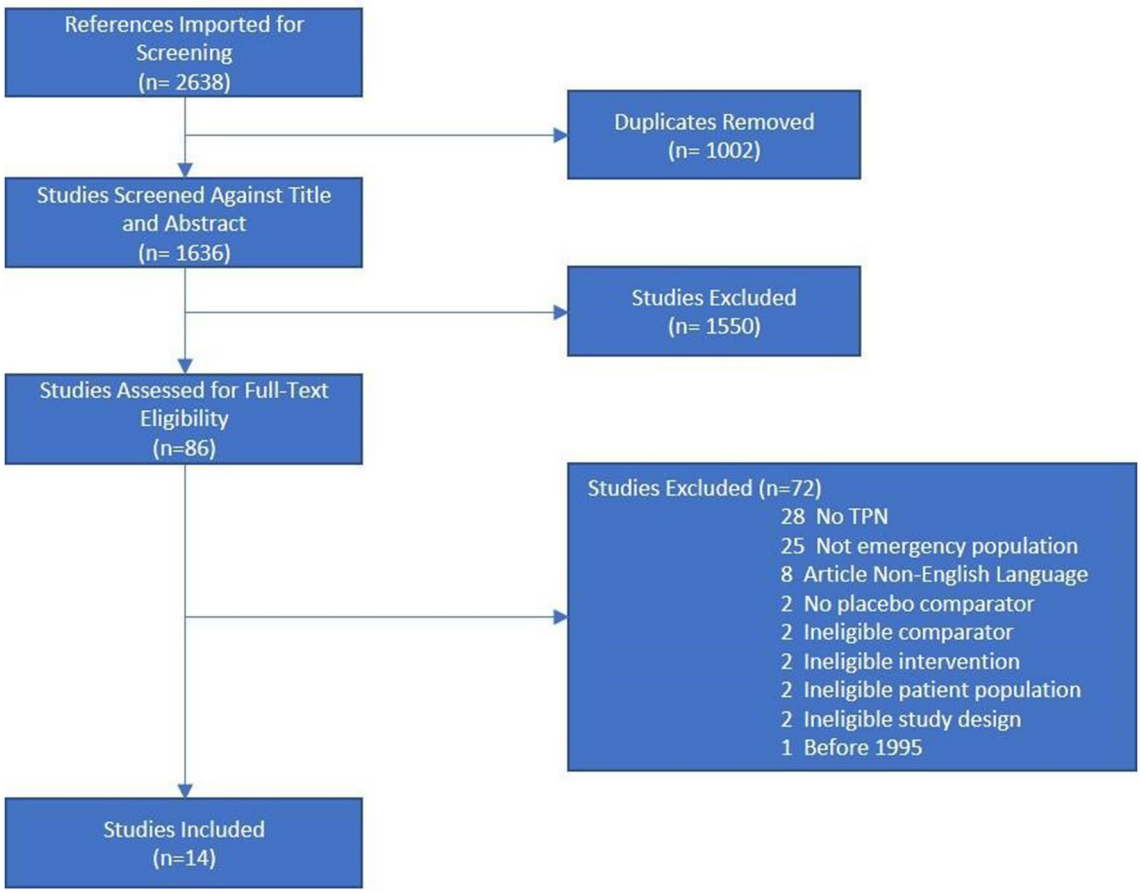


Fig. 1 PRISMA flow diagram

PN to PN with variable doses of amino acids based upon blood tests [29] (Table 1/Fig. 2).

Four studies reported mortality [18, 19, 22, 25, 27], some within hospital others at 6-month follow-up, those with the same intervention and control arms have been meta-analysed below; seven trials reported new-onset or hospital-acquired infections [1, 18, 21, 22, 25, 27, 28]; seven trials reported length of stay [18, 19, 21, 22, 25, 27, 28], and four trials reported nitrogen balance [21, 24, 27, 29] (Table 2). A summary of all reported outcomes is presented in Table S1.

Risk of bias within studies

Two studies had high risk and six an unclear risk of bias from the sequence generation method. Three studies had a high and seven an unclear risk of bias from the allocation concealment method. Five trials had high-risk methods of blinding patients and clinicians, half had a low risk. Six studies had high-risk blinding of assessments and two studies were unclear. No study had a high risk

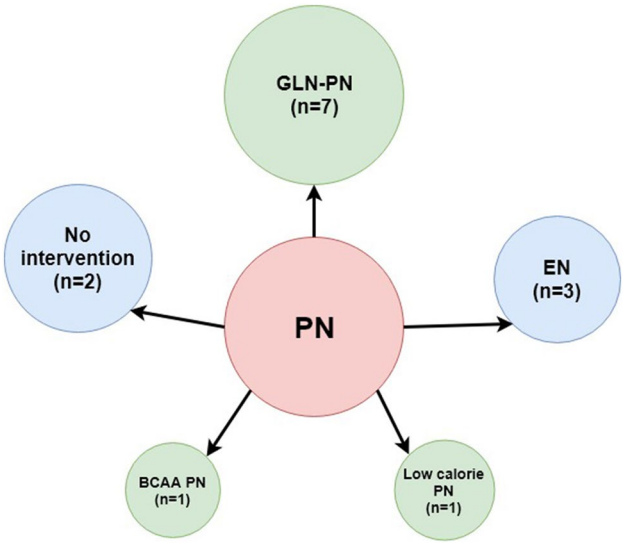


Fig. 2 Summary of comparisons identified. *EN* enteral nutrition, *PN* parenteral nutrition, *BCAA* branched chain amino acid, *GLN-PN* glutamine supplimented parenteral nutrition

Table 1 Summary of study characteristics

Author (year)	Population	Total population (*N*)	Intervention	Control
Ahrens (2005) [1]	Consecutive patients requiring parenteral nutrition in a level I trauma centre	40	Low-calorie PN	Standard-calorie PN
Antebi (2003) [17]	ICU patients undergoing major abdominal surgery	20	SMOF PN regimen	LIPOVEN PN regimen
Berard (2002) [29]	Surgical intensive care patients (SICU), requiring PN for 10 days	13	5 day PN as standard, 5 days PN individualised	10-day PN
Chen (2017) [28]	Confirmed gastric outlet obstruction patients	68	PN 7 days preoperatively	Increasing EN 14 days before surgery
Estivariz (2008) [18]	Pancreatitic and non-pancreatitic surgical intensive care patients requiring PN	59	GLN-PN	GLN-free PN
Goeters (2002) [19]	Post-operative intensive care unit	163	Al-Gln-supplemented PN	GLN-free PN
Hu (2003) [26]	Post-operative patients with impaired liver function (Child B or C)	35	PN or EN (via jejunostomy)	No nutritional intervention
Hulsewe (2004) [20]	Nutritionally depleted gastrointestinal surgery patients	24	Glycyl-glutamine supplemented PN	Isonitrogenous control solution PN
Jiang (1999) [21]	Major gastrointestinal surgery patients requiring PN for 6 days	120	Al-Gln supplemented PN	GLN-free PN
Luo (2008) [23]	Surgical intensive care patients		GLN-PN	GLN-free PN
Malhotra (2004) [27]	Emergency surgery for peritonitis following gut perforation	169	PN	EN (NG feed)
Powell-Tuck (1999) [22]	Patients requiring PN, surgical subgroup reported	168	GLN-PN	PN
Wang (2003) [24]	Major abdominal Surgery including trauma	40	PN with BCAA	PN with AA
Ziegler (2016) [18]	Surgical intensive care patients requiring PN	150	GLN-PN	Standard PN

PN parenteral nutrition, *EN* enteral nutrition, *Al* alanine, *GLN-PN* glutamine-supplemented PN

Table 2 Study comparators and outcomes

	In-hospital mortality	Length of stay	HAI	Weight change	Mechanistic data, e.g. nitrogen balance
PN vs EN					
Malhotra [27]	✓	✓	✓	✓	✓
Chen [28]	–	✓	✓	✓	–
Hu [26]	–	–	–	✓	✓
PN-GLN vs PN					
Estivariz [18]	✓	✓	✓	–	–
Goeters [19]	✓	✓	–	–	–
Jiang [21]	–	✓	✓	–	✓
Powell-tuck [22]	✓	✓	✓	–	✓
Ziegler [25]	✓	✓	✓	–	✓
Hulsewe [20]	–	–	–	✓	✓
Luo [23]	–	–	–	✓	✓
PN vs standard care					
Berard [29]	–	–	–	–	✓
Hu [26]	–	–	–	–	✓
BCAA-PN vs PN-AA					
Wang [24]	–	–	–	–	✓
SMOF-PN vs Lipoven					
Antebi [17]	–	–	–	–	✓
Low calories PN vs standard calories PN					
Ahrens [1]	–	–	✓	–	–

Tick shows that outcome was assessed for. *HAI* hospital-acquired infections, *PN* parenteral nutrition, *EN* enteral nutrition, *BCAA* branched-chain amino acids

of incomplete data and two trials were unclear. One trial had a high risk of selective reporting. Five studies had a high risk of other bias and five an unclear risk. Trials with control variables of EN or control (standard nutritional care) are open studies [26, 28]. Many of the trials had no statement of conflict of interest or funding sources while many others were funded by medical intervention manufacturers (Figs. 3, 4).

Synthesis of results

Mortality

In the comparison of PN-GLN to PN (4 studies, 413 patients, Fig. 5), GLN-supplemented PN reduced risk of mortality by 8% (risk difference (RD) − 0.08, 95% CI − 0.17 to 0.01, $p = 0.08$), but this was not statistically significant. Statistical heterogeneity was low ($I^2 = 22\%$). The one trial comparing PN to EN did not observe a statistically significant reduction in death (RD − 0.05, 95% CI− 0.17 to 0.06, $p = 0.37$) [27].

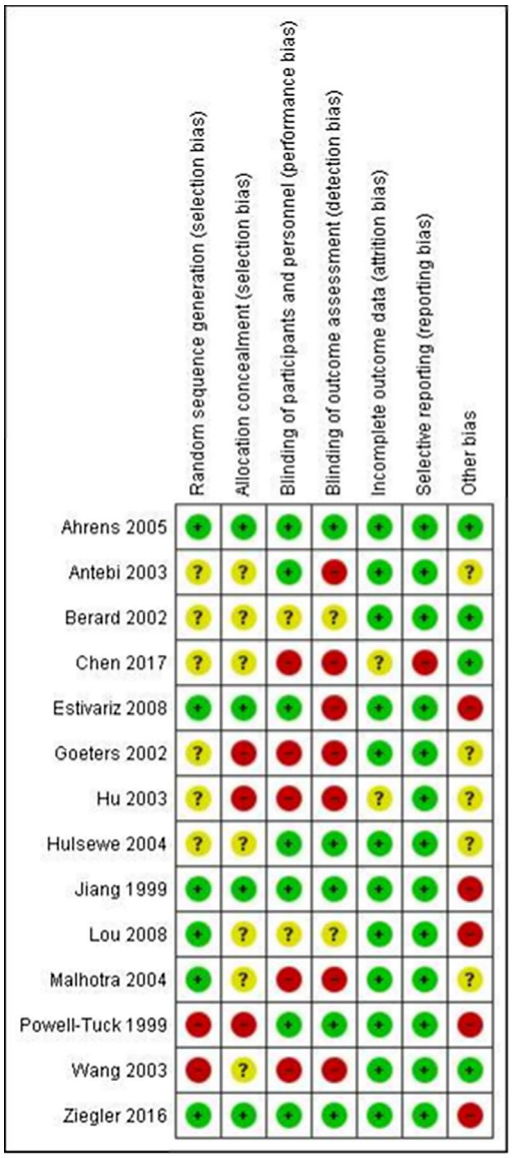
Length of hospital stay

In the comparison of PN to EN, Malhotra showed no significant reduction in LOS (mean difference − 0.11 days, 95% CI − 1.17 to 1.39, $p = 0.085$) [27]. Chen provided no confidence intervals; however, found a significant reduction in LOS for the PN group [28]. Meta-analysis comparing the effect of PN-GLN to PN in length of hospital stay (5 studies, 474 patients, Fig. 6) found a trend towards reduced LOS in the glutamine-supplemented group (mean difference − 2.4, 95%CI − 7.19 to 2.32 days). This was associated with high heterogeneity ($I^2 = 92$).

Hospital-acquired infections

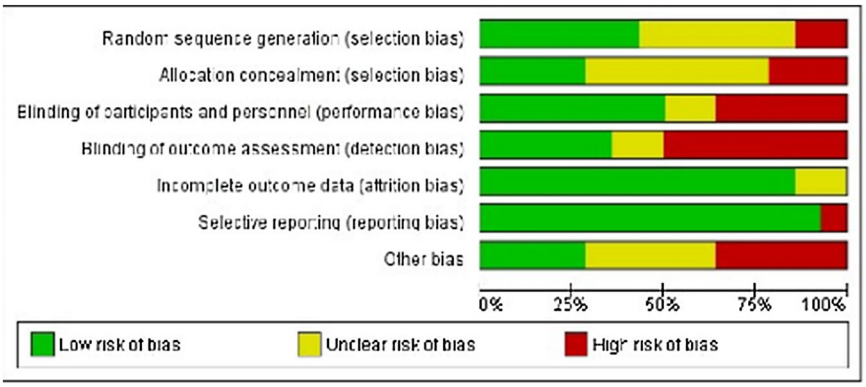
Seven studies reported HAI as an outcome. One study comparing low-calorie PN to high-calorie PN, found no significant reduction in HAI [1]. Two studies compared PN to EN ($n = 232$). Chen found a significant increase in HAI with PN, but data are incomplete, preventing further interpretation [28]. Malhotra found a non-significant reduction in HAI with the use of PN (relative risk = 0.66, 95% CI 0.407–1.091, $p = 0.103$) [27].

Fig. 3 Risk of bias summary



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Fig. 4 Risk of bias graph



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

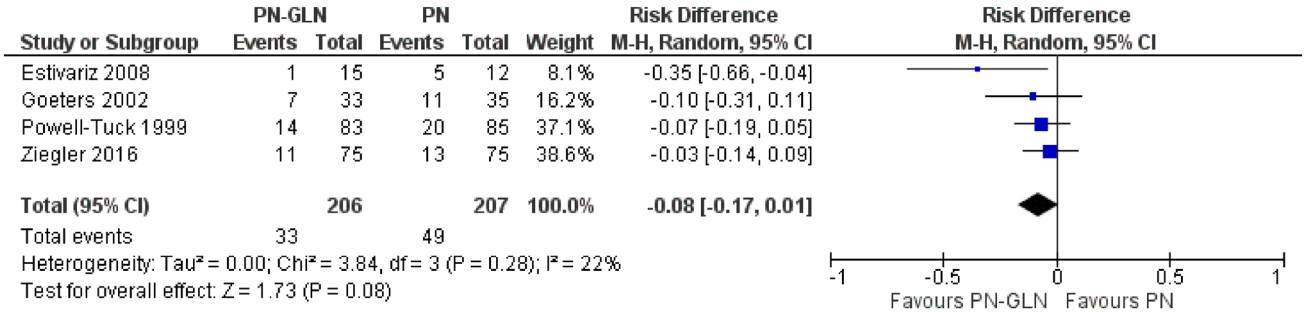


Fig. 5 Meta-analysis of in-hospital mortality, PN-GLN (glutamine-supplemented parenteral nutrition), PN (parenteral nutrition), CI (confidence intervals), and SD (standard deviation)

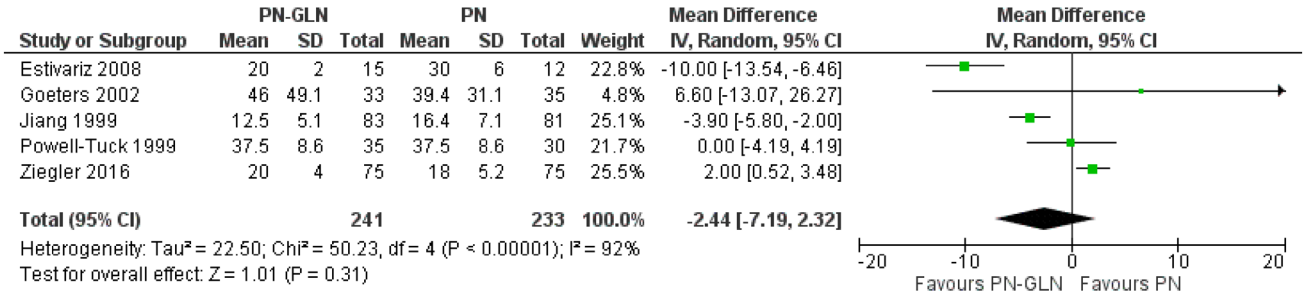


Fig. 6 Meta-analysis of length of stay, PN-GLN (glutamine-supplemented parenteral nutrition), PN (parenteral nutrition), CI (confidence intervals), SD (standard deviation)

Nitrogen balance

Five studies reported nitrogen balance, two of which compared PN to no-nutritional intervention ($n=83$). Berard reported no significance, with no confidence intervals given [29]; Hu reported a significant improvement but with no confidence intervals [26]. Two studies compared PN to EN ($n=269$), Malhotra found a significant benefit with PN (88% population difference, $p<0.05$) [27]; Hu found a significant benefit with EN [26], but neither gave confidence intervals. One study comparing PN with branched-chain amino acids (BCAA) and PN with amino acids ($n=40$) found patients achieved positive nitrogen balance significantly quicker in the BCAA-supplemented group, confidence intervals not given ($p<0.05$) [24].

Weight change

Four studies reported on weight change. Three studies compared PN to EN ($n=337$): Chen made no statistical comparison between the interventions [28]; Hulsewe reported no significant result and gives no data [20]; Hu reported no significant difference between groups (mean difference −0.3 kg) [26]; Malhotra found a significant reduction in weight loss with PN (mean difference = 2 kg, 95% CI −1.54 to 2.46, $p<0.0001$) [27]. One study comparing PN to no-nutrition intervention ($n=70$) reported a significant difference without confidence intervals (PN mean weight loss -2.4 ± 1.1 kg, control -3.3 ± 1.7, $p<0.05$.) [26]. Malhotra reported a greater weight loss in the intervention group than control ($p<0.05$) [27]; however, this study included patients with faecal peritonitis who may have been more critically ill than those in any other study included.

Risk of bias across studies

For the outcome of death, GRADE assessment found the risk of bias across studies comparing PN-GLN to PN to be high. This was due to a lack of allocation concealment information, and imprecision in results. In trials comparing PN to EN, there is a high risk of bias as due to the methodology of being an open trial, they cannot be blinded. A number of other concerns were noted including small population sizes, and the roles of funding sources [30]. The GRADE assessment is presented in Table 3.

Discussion

This review suggests there may be benefit from the use of PN in the critically ill surgical patient with gastrointestinal failure, in terms of reduced LOS. The effect of PN

Table 3 GRADE PRO—risk of bias across studies

Certainty assessment							No. of patients Number of events/total participants (percentage)		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PN-GLN	Standard PN	Relative (95% CI)	Absolute (95% CI)		
PN-GLN compared to standard PN for critically ill surgical patients and associated mortality rates												
Death—PN-GLN vs standard PN (follow-up: median 28)												
4	Randomised trials	Serious [a]	Not serious	Not serious	Serious [b]	None	33/239 (13.8%)	48/233 (20.6%)	**RR 0.70** (0.47 to 1.04)	**62 fewer per 1000** (from 8 more to 109 fewer)	⨁⨁◯◯ LOW	CRITICAL
PN compared to EN for critically ill surgical population and associated mortality rates												
Death												
1	Randomised trials	Serious [c]	Not serious	Not serious	Serious [d]	None	12/83 (14.5%)	16/81 (19.8%)	**RR 0.660** (0.700 to 1.091)	**67 fewer per 1000** (from 18 more to 59 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI confidence interval, *RR* risk ratio, *PN* parenteral nutrition, *PN-GLN* glutamine-supplemented parenteral nutrition, *EN* enteral nutrition

[a]Allocation concealment and random sequence generation was a high risk in two studies

[b]Estivariz has significantly wider confidence intervals than other studies

[c]A single-blinded trial, with unclear allocation concealment

[d]Wide 95% confidence intervals (− 5.78 to 13.68)

on HAIs is not clear, and there is no clear mortality benefit. The literature is based upon small trials with a high level of heterogeneity and bias and should be interpreted accordingly. There is, however, signal that some forms of PN may offer benefits to the critically ill surgical patient.

The body of literature addressing nutritional support in acutely ill surgical patients is limited; it includes many heterogenous populations, small trials, with heterogeneity of interventions and outcomes. This makes robust assessment challenging. Critically, there are few, if any, trials of PN vs no nutritional support or placebo control, making it difficult to estimate the absolute benefit of nutritional intervention in this setting. Trials of PN in the intensive care population have failed to show consistent significant benefit [31], although these trials included patients with functioning gastrointestinal tracts/non-surgical patients where enteral nutrition might be preferable. A recent pilot trial signalled that the surgical subgroup of patients may derive greater benefit from PN-based interventions than medical comparators [32]. The evidence base is also limited as recruitment to trials in the emergency surgical setting can be challenging—further thought is needed on how best to tackle this problem, otherwise we may not be able to tease out the true effect of nutritional support in the critically ill surgical patient. This study focussed on the role of PN in patients following surgery, and not in the treatment of patients with complications such as anastomotic leak or enterocutaneous fistula, where its role is more defined [6].

The effect of interventions on mortality suggests a modest benefit of PN, particularly glutamine-supplemented PN. This is mechanistically plausible as PN may arrest the catabolic phase and provide calories avoiding cellular exhaustion [33]. Our finding of a potentially reduced LOS is at odds with some reviews [34], although studies of patients in intensive care have shown benefit in PN reducing LOS [35]. Preoperative PN has a known association with shorter postoperative LOS in elective patients [36]. Additional benefits for PN-GLN may come from the antioxidant properties of glutamine as a substrate for synthesis of glutathione [37, 38], and its reported role in preservation of the intestinal epithelial barrier through enterocyte nutrition [39]. Additionally, glutamine is also a substrate for gluconeogenesis in the liver and may support mobilisation of energy reserves [40]. Reviews of recent trials have challenged the benefit of glutamine supplementation [41], and it has fallen out of favour to some extent [42]. In variance with the intensive care literature, the consistent benefit of glutamine supplementation of PN is seen in other acute surgical conditions such as acute pancreatitis (which was not included in this study) [43]. This may suggest that glutamine offers benefits to patients with gastrointestinal pathology, perhaps from the proposed benefits for enterocytes. Alternatively, there may be fundamental differences in the design, conduct, and outcome measures used in the different trials which guide us to incorrect conclusions.

Qualitative assessment of the association between nutritional intervention and HAIs suggests a possibility of benefit. Unfortunately, as varying outcomes and definitions were used across studies, we were unable to pool these data for meta-analysis. A reduction in HAIs is a plausible effect as there is evidence linking infections with acute malnutrition due to the inadequate response of the immune system [44]. This correlates with other reviews and studies reviewing malnutrition in intensive care populations, in elderly populations and in cancer patients where malnutrition is common [45–48].

Current guidelines advocate the use of EN where possible in surgical patients, where they are able to tolerate feed and do not have contraindications such as perforation, fistula or ischaemia [6, 9]. They advise the use of PN in patients who have been without enteral nutrition for 5–7 days, with hypermetabolic state or significant malnutrition, and also where there is likely to be a significant duration of parenteral therapy (> 7 days) [7, 9]. There is moderate-to-low evidence supporting the use of supplements such as fish oils or arginine for their immunomodulation properties in postoperative patients [9]. As previously, it is important to note that most of this evidence comes from either medical intensive care or patients undergoing elective surgery, so generalisability may be limited.

Special consideration must be given to the effect of hyperglycaemia in critical illness. This may be observed during therapy with PN, and the associated hyperglycaemia has been shown to cause significantly higher rates of morbidity in the intensive care population [49]. The study reporting this finding was published in 2006. All but one study in this review were published before this date, and glycaemic management, therefore, may not have been optimal. This is one change in practice that might alter the findings if some of these studies were repeated today. Current guidance advocates close monitoring and intervention in hyperglycaemia [9].

There are several limitations to this systematic review, primarily the limited body of studies relevant to our population; however, a review is only as good as the literature upon which it is based. There is a high level of bias for some of the included trials, with concerns related to funding. Bias, reliability and the small size of studies may affect validity of many of the trials available [50]. There are also many different outcome measures across the trials; these often are non-comparable due to different interventions or comparators, e.g. HAIs, making pooling difficult. There may also be differences in the preparation of PN used, and the calculations used to estimate caloric need

[51], leading to variation in the interventions and subsequent outcomes [52]. However, the review is a robust systematic review that was conducted methodically with reference to the Cochrane handbook, and used best practice bias assessment with Cochrane Risk of Bias tool and GRADE PRO. Whilst it does not tell us clearly that PN is of significant value vs no nutrition, it does highlight that further research is required.

The outcomes reported in this review—mortality, hospital-acquired infections and length of stay—are important for patients and clinicians alike. PN is a mechanistically plausible intervention to improve these outcomes in the critically ill surgical patient. There is uncertainty about the true effect of PN in this population, meaning there is a clear need for randomised controlled trials. Key questions that research should answer include (i) whether PN offers benefit to the patient group compared to no nutrition support, (ii) whether early PN (e.g. < 24 h from admission) is better than delayed PN (e.g. 5 days or more after admission), (iii) whether glutamine supplementation offers clear benefit to this patient group, and (iv) what are the characteristics of patients who might benefit from these interventions. These studies should use patient and clinician important outcomes (e.g. quality of life, complications) rather than mechanistic outcomes (e.g. nitrogen balance) to determine if they are of tangible benefit.

Conclusions

In critically ill surgical patients, the use of PN may offer benefit in key outcomes. The size and quality of the studies lead to considerable uncertainty around the estimates of clinical effect, meaning a large-scale randomised controlled trial is required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

Informed consent Informed consent is not required.

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