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

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/137487/

Version: Published Version

**Article:**
Ledgard, K., Mann, B.S., Hind, D. orcid.org/0000-0002-6409-4793 et al. (1 more author) (2018) What is the evidence for the use of parenteral nutrition (PN) in critically ill surgical patients: a systematic review and meta-analysis. Techniques in Coloproctology, 22 (10). pp. 755-766. ISSN 1123-6337

https://doi.org/10.1007/s10151-018-1875-1

---

**Reuse**
This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:
https://creativecommons.org/licenses/

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

---

White Rose Research Online
University of Sheffield
Universities of Leeds, Sheffield & York

---

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/
What is the evidence for the use of parenteral nutrition (PN) in critically ill surgical patients: a systematic review and meta-analysis

K. Ledgard1 · B. Mann1 · D. Hind2 · M. J. Lee1,3

Received: 30 May 2018 / Accepted: 8 November 2018 / Published online: 14 November 2018
© The Author(s) 2018

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, I² = 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
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 of bias from the blinding of outcome assessment.

**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] | Pancreatic and non-pancreatic 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           |
| Hulsewé (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                                            | 169                  | GLN-PN                              | GLN-free PN                          |
| Malhotra (2004) [27] | Emergency surgery for peritonitis following gut perforation                | 150                  | PN                                  | EN (NG feed)                         |
| Powell-Tuck (1999) [22] | Patients requiring PN, surgical subgroup reported                           | 150                  | GLN-PN                              | Standard PN                          |

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

PN parenteral nutrition, EN enteral nutrition, AI alanine, GLN-PN glutamine-supplemented PN

© Springer
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-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].

**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].

---

**Table 2** Study comparators and outcomes

| 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.
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.
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 $-2.4\pm1.1$ kg, control $-3.3\pm1.7$, $p<0.05$.) [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 | Effect | Certainty | Importance |
|----------------------|-----------------|--------|-----------|------------|
|                      | Number of events/total participants (percentage) | 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)

| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | PN-GLN | Standard PN | Relative (95% CI) | Absolute (95% CI) |
|----------------|--------------|--------------|---------------|--------------|-------------|---------------------|--------|-------------|-----------------|------------------|
| 4              | Randomised   | 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) |

PN compared to EN for critically ill surgical population and associated mortality rates

Death

| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | PN-GLN | Standard PN | Relative (95% CI) | Absolute (95% CI) |
|----------------|--------------|--------------|---------------|--------------|-------------|---------------------|--------|-------------|-----------------|------------------|
| 1              | Randomised   | 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) |

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 enteroctaneous 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.

**Acknowledgements** The authors are grateful to Adele Sayers and Stephen Chapman for their constructive feedback on the manuscript.

**Funding** No funding was received for this study.

**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.

**Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

**References**

1. Ahrens CL, Barletta JF, Kanji S et al (2005) Effect of low-calorie parental nutrition on the incidence and severity of hyperglycemia in surgical patients: a randomized, controlled trial. Crit Care Med 33:2507–2512. https://doi.org/10.1097/01.CCM.0000186746.64572.8A
2. Buchman AL, Ament ME, Sohle M et al (2001) Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. JPEN. https://doi.org/10.1177/01486071010372391
3. Buzby GP, Colling CL, Crosb LO, Al E (1991) Perioperative total parenteral nutrition in surgical patients. N Engl J Med 325:525–532. https://doi.org/10.1056/NEJM199108223250801
4. Drover JW, Cahill NE, Kutsogiannis J et al (2015) Nutrition therapy for the critically ill surgical patient: we need to do better! JPEN 34:644–652. https://doi.org/10.1177/0148607110372391
5. Wollhuis AM, Bislenghi G, Fieuws S et al (2016) Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. Color Res Dis 18:01–09. https://doi.org/10.1111/codi.13210
6. ESCP Intestinal Failure Group (2016) European Society of Coloproctology consensus on the surgical management of intestinal failure in adults. Color Res Dis 18:535–548. https://doi.org/10.1111/codi.13321
7. NICE (2006) Clinical Guideline 32: Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. https://www.nice.org.uk/guidance/cg32. Accessed 12 Nov 2018
8. Singer P, Berger MM, Van den Bergh G et al (2009) ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 28:387–400. https://doi.org/10.1016/j.clnu.2009.04.024
9. McClave SA, Taylor BE, Martindale RG et al (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr 40:159–211. https://doi.org/10.1177/0148607115621863
10. Gunst J, Van den Bergh G (2017) Parenteral nutrition in the critically ill. Curr Opin Crit Care 23:149–158
11. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group (1992) Perioperative total parenteral nutrition in surgical patients. N Engl J Med 327:70–75. https://doi.org/10.1056/NEJM199207093207020
12. NASBO (2017) Annual report of the national audit of small bowel obstruction 2017. http://nasbo.org.uk/wp-content/uploads/2017/11/NASBO-web.pdf. Accessed 12 Nov 2018
13. Higgins JPT, Green S (eds) (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://www.hanbook.cochrane.org/
14. Knobloch K, Yoon U, Vogt PM (2011) Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J Cognit Maxillodent Surg 39:91–92. https://doi.org/10.1016/j.jcms.2010.11.001
15. Tessari P (2006) In: Mantovani G, Anker SD, Inui A et al (eds) Nitrogen balance and protein requirements: definition and measurements BT—cachexia and wasting: a modern approach. Springer Milan, Milano, pp 73–79
16. Schüinemann H, Brožek J, Guyatt G, Oxman A (eds) (2013) GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from https://www.guidelinevelopment.org/handbook

17. Antébi H, Mansoor O, Ferrier C et al (2004) Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. J Parenter Enter Nutr 28:142–148

18. Estivariz CF, Griffith DP, Luo M et al (2008) Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. J Parenter Enter Nutr 32:389–402. https://doi.org/10.1177/0148607081377880

19. Goetters C, Wenn A, Mertes N et al (2002) Parenteral 1,alanyl-1-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 30:2032–2037. https://doi.org/10.1097/01.CCM.0000025908.95498.A3

20. Hulsewé KWE, van Acker BAC, Hameeteman W et al (2004) Influence of enteral nutrition from nasal feeding tubes on gastric outlet obstruction. Techniques in Coloproctology (2018) 22:755–766

21. Jiang ZM, Cao JD, Zhu XG et al (1999) The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. J Parenter Enter Nutr 23:562–566. https://doi.org/10.1177/014860719902300516

22. Powell-Tuck J, Jamieson C, Bettany GE et al (1999) A double-blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. Gut 45:82–88

23. Luo M, Fernandez-Estivariz C, Jones DP et al (2008) Depletion of plasma antioxidants in surgical intensive care unit patients requiring parenteral feeding: effects of parenteral nutrition with or without alanyl-glutamine dipeptide supplementation. Nutrition 24:37–44. https://doi.org/10.1016/j.nut.2007.10.004

24. Wang X-Y, Ni N, Gu J et al (2003) The effects of the formula of amino acids enriched BCAA on nutritional support in traumatic patients. World J Gastroenterol 9:599–602

25. Ziegler TR, May AK, Hebar G et al (2016) Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients. Ann Surg 263:646–655. https://doi.org/10.1097/SLA.0000000000001497

26. Hu Q-G, Zheng Q-C (2003) The influence of enteral nutrition in postoperative patients with poor liver function. World J Gastroenterol 9:843–846

27. Mallhotra A, Mathur AK, Gupta S et al (2004) Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. J Postgrad Med 50:102–106

28. Chen Z, Lin S, Dai Q et al (2017) The effects of pre-operative enteral nutrition from nasal feeding tubes on gastric outlet obstruction. Nutrients 9:373. https://doi.org/10.3390/nu9040373

29. Berard M, Pelletier A, Ollivier J et al (2002) Qualitative manipulation of amino acid supply during total parenteral nutrition in surgical patients. J Parenter Enter Nutr 26:136–143. https://doi.org/10.1177/0148607102026002136

30. Falk Delgado A, Falk Delgado A (2017) The association of funding source on effect size in randomized controlled trials: 2013–2015—a cross-sectional survey and meta-analysis. Trials 18:125. https://doi.org/10.1186/s13063-017-1872-0

31. Elke G, van Zanten ARH, Lemieux M et al (2016) Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 20:117. https://doi.org/10.1186/s13054-016-1298-1

32. Wischmeyer PE, Hassellmann M, Kummerlen C et al (2017) A randomized trial of supplemental parenteral nutrition in overweight and obesity critically ill patients: the TOP-UP pilot trial. Crit Care 21:142. https://doi.org/10.1186/s13054-017-1736-8

33. Tamiya H, Yasunaga H, Matusi H et al (2015) Comparison of short-term morbidity and morbidity between parenteral and enteral nutrition for adults without cancer: a propensity-matched analysis using a national inpatient database. Am J Clin Nutr 102:1222–1228. https://doi.org/10.3945/ajcn.115.111831

34. Bally MR, Blaser Yildirim PZ, Bounouir L et al (2016) Nutritional support and outcomes in malnourished medical inpatients: a systematic review and meta-analysis. JAMA Intern Med 176:43–53. https://doi.org/10.1001/jamainternmed.2015.6587

35. Fuentes-Carrazco M, de Anda GV, Denova-Gutiérrez E (2008) P019 nutritional support in critically ill patients decreases the length of stay and the mortality rate in the ICU. Clin Nutr Suppl 3:37. https://doi.org/10.1016/S1744-1161(08)70081-4

36. Jie B, Jiang Z-M, Nolan MT et al (2012) Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk. Nutrition 28:1022–1027. https://doi. org/10.1016/j.nut.2012.01.017

37. van Stijn MFM, Ligthart-Melis GC, Boelens PG et al (2008) Antioxidant enriched enteral nutrition and oxidative stress after major gastrointestinal tract surgery. World J Gastroenterol 14:6960–6969. https://doi.org/10.3748/wjg.14.6960

38. Abild JS, Pérez R, Castaño J et al (2008) P020 effects of supply with glutamine on antioxidant system in patients with parenteral nutrition. Clin Nutr Suppl 3:37. https://doi.org/10.1016/S1744 -1161(08)70082-6

39. Ziegler TR, Bazargan N, Leader LM, Martindale RG (2000) Glutamine and the gastrointestinal tract. Curr Opin Clin Nutr Metab Care 3:355–362

40. Matés JM, Pérez-gómez C, Núñez J et al (2002) Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death. Int J Biochem Cell Biol 34:439–458

41. van Zanten ARH, Hofman Z, Heyland DK (2015) Consequences of the REDOXs and METAPLUS trials: the end of an era of glutamine and antioxidant supplementation for critically ill patients? J Parenter Enteral Nutr 39:890–892. https://doi.org/10.1177/0148607115467201

42. Wischmeyer P (2015) Glutamine supplementation in parenteral nutrition and Intensive Care Unit patients. J Parenter Enter Nutr 39:893–897. https://doi.org/10.1177/0148607115539792

43. Asrani V, Chang W, Dong Z et al (2013) Glutamine supplementation in acute pancreatitis: a meta-analysis of randomized controlled trials. Pancreatology 13:468–474

44. Schäible UE, Kaufmann SHE (2007) Malnutrition and infection: complex mechanisms and global impacts. PLoS Med 4:0806–0812. https://doi.org/10.1371/journal.pmed.0040115

45. Unosson M, Ek AC, Bjurrul P, Larsson J (1990) Effect of dietary supplement on functional parameters in geriatric patients. Clin Nutr 9:42. https://doi.org/10.1016/S1744-1161(09)70027-4

46. Asper JM, Lildo LO, Sinamban R et al (2009) Effect on immune indices of preoperative intravenous glutamine dipeptide supplementation in malnourished abdominal surgery patients in the pre-operative and postoperative periods. Nutrition 25:920–925. https://doi.org/10.1016/j.nut.2009.01.014

47. Aghaepour N, Kin C, Gaino EA et al (2017) Deep immune profiling of an arginine-enriched nutritional intervention in patients undergoing surgery. J Immunol. https://doi.org/10.4049/jimmu no 1700421

48. Beier-Holgersen R, Brandsrup B (1999) Influence of early postoperative enteral nutrition versus placebo on cell-mediated immunity, as measured with the Multitest® CMI. Scand J Gastroenterol 34:98–102. https://doi.org/10.1080/00365529950172907

49. Van den Berghe G, Wilm R, Ghuysen A et al (2001) Intensive insulin therapy in the medical ICU. N Engl J Med 345:449–461. https://doi.org/10.1056/NEJMoa1109400
50. Faber J, Fonseca LM (2014) How sample size influences research outcomes. Dental Press J Orthod 19:27–29. https://doi.org/10.1590/2176-9451.19.4.027-029.ebo

51. Fraipont V, Preiser J-C (2013) Energy estimation and measurement in critically ill patients. JPEN J Parenter Enter Nutr 37:705–713

52. Alberda C, Gramlich L, Jones N et al (2009) The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 35:1728–1737. https://doi.org/10.1007/s00134-009-1567-4