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REVIEW

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# Impact of Intravenous Fluids and Enteral Nutrition on the Severity of Gastrointestinal Dysfunction: A Systematic Review and Meta-analysis

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## Abstract

**Introduction**: Gastrointestinal dysfunction (GDF) is one of the primary causes of morbidity and mortality in critically ill patients. Intensive care interventions, such as intravenous fluids and enteral feeding, can exacerbate GDF. There exists a paucity of high-quality literature on the interaction between these two modalities (intravenous fluids and enteral feeding) as a combined therapy on its impact on GDF. **Aim**: To review the impact of intravenous fluids and enteral nutrition individually on determinants of gut function and implications in clinical practice. **Methods**: Randomized controlled trials on intravenous fluids and enteral feeding on GDF were identified by a comprehensive database search of MEDLINE and EMBASE. Extraction of data was conducted for study characteristics, provision of fluids or feeding in both groups and quality of studies was assessed using the Cochrane criteria. A random-effects model was applied to estimate the impact of these interventions across the spectrum of GDF severity. **Results**: Restricted/ goal-directed intravenous fluid therapy is likely to reduce 'mild' GDF such as vomiting ($p = 0.03$) compared to a standard/ liberal intravenous fluid regime. Enterally fed patients experienced increased episodes of vomiting ($p = <0.01$) but were less likely to develop an anastomotic leak ($p = 0.03$) and peritonitis ($p = 0.03$) compared to parenterally fed patients. Vomiting ($p = <0.01$) and anastomotic leak ($p = 0.04$) were significantly lower in the early enteral feeding group. **Conclusions**: There is less emphasis on the combined approach of intravenous fluid resuscitation and enteral feeding in critically ill patients. Conservative fluid resuscitation and aggressive enteral feeding are presumably key factors contributing to severe life-threatening GDF. Future trials should evaluate the impact of cross-interaction between conservative and aggressive modes of these two interventions on the severity of GDF.

**Keywords**: gastrointestinal dysfunction, gastrointestinal failure, critical illness, surgical, intravenous fluids, resuscitation, enteral feeding

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## Introduction

Gut dysfunction (GDF) is a common problem in critically ill patients. It is the leading cause of multiple organ dysfunction syndrome/failure (MODS/MOF) and a significant cause of mortality and morbidity in critically ill patients [1]. In addition to this, the treatment of acute and critical illness can exacerbate GDF. Commonly used ICU interventions such as intravenous fluid resuscitation, early aggressive enteral feeding and vasopressor therapy are key factors leading to a secondary gut injury. In critical illness, intravenous fluid is the mainstay of early management for hemodynamic instability. It is vital to resuscitate a patient before commencing vasopressor therapy, particularly to delay the onset of an ischemic insult commonly occurring in hemodynamically unstable patients [2]. On the flip side, over-resuscitation can lead to bowel oede-

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ma leading to an ileus, while under-resuscitation with persistent splanchnic and peripheral vasoconstriction can trigger intestinal mucosal ischemia [3]. Although, enteral nutrition is the preferred approach to meet nutritional and modest fluid requirements in these patients, the delivery of early but aggressive enteral nutrition (EN) in hemodynamically unstable patients can precipitate the development of severe GDF, potentially leading to non-occlusive mesenteric ischemia which increases the chance of sepsis, multi-organ failure and mortality [4]. Intravenous fluid and enteral nutrition are two sides of the same coin and play a crucial role in determining the outcome of GDF if used wisely. However, very few studies have evaluated the role of these two modalities, thus making it difficult to understand their relationship with relevance to the severity of GDF. The aim was to review the evidence of the impact of intravenous fluid resuscitation and enteral nutrition individually on determinants of gut function and the implications in clinical practice.

## Methods

### Search Criteria and Study Identification

Electronic databases (MEDLINE and EMBASE) were searched using keywords on 'gastrointestinal dysfunction in adult intensive care unit (ICU) /surgical patients on enteral feeding and intravenous fluids. The databases screened for all publications from the earliest available until 16th October 2018 (Appendix A).

Randomised controlled trials were searched by applying the keywords. Any additional studies on the impact of 'intravenous fluid' and 'enteral feeding' were included in the screening for the systematic review and meta-analysis. The search identification, screening and selection were conducted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart (Fig1) [5]. The study selection criteria were as follows.

The inclusion criteria were:

*Study design*: all randomised controlled trials (intravenous fluids and enteral feeding on GDF);

*Study population*: Adult surgical and critically ill patients

*Disease state*: critical illness and postoperative conditions

*Intervention*: **enteral feeding:** route of feeding (enteral vs parenteral); timing of feeding (early vs delayed); feeding vs nil-by-mouth and **intravenous fluids**: restricted vs liberal regime, goal-directed vs standard/conventional, low-infusions vs high-infusion or controlled vs rapid fluid therapy; intravenous fluids type: crystalloid fluid (normal saline or plasmalyte or ringer's lactate) or colloid fluid (hydroxyethyl starch, albumin, gelofusion).

*Study outcome*: the occurrence of gastrointestinal dysfunction

The studies were excluded if they were:

- non-ICU or non-surgical patients
- paediatric population
- animal studies
- published in non-English languages
- conducted on healthy volunteers
- non-randomized trials (intravenous fluid therapy and enteral feeding)
- not relevant to either of the interventions planned to study pattern of feeding (bolus vs continuous), comparative feed compositions (standard vs immune-enriched), related routes of feeding (nasogastric vs nasojejunal or jejunal) and studies addressing medications (e.g. prokinetic therapy).

*Data Extraction*: Data were extracted and independently recorded by two authors using predesigned data collection forms on Microsoft Excel.

Study characteristics included baseline demographic data such as author, publication year, study setting (ICU or surgical ward), admission diagnosis, study population, the total number of patients, fluid or enteral feeding interventions applied to experimental and control groups. The effect of fluid therapy and enteral feeding on GDF was analysed by separating the severity of GDF outcomes: 1) *mild to moderate* and 2) *moderate to severe*. All studies were stratified into the Clavien-Dindo classification [6] depending on the variability of clinical aetiology and interventions applied. Any additional studies derived from other sources and reference lists of included articles were screened and included if relevant. Data were independently reviewed and cross-checked by two authors (V.A. and A.B.). Any inconsistencies or disagreements were discussed between the two authors (V.A. and A.B.), and differences of opinion were further clarified by the senior author (J.A.W.).

### Methodological quality

The methodological quality of included randomised controlled trials was assessed according to the

Cochrane recommendations (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) [7]. These included systematic differences between groups (selection bias and performance bias), blinding of study participants and assessors, sequence allocation and concealment of allocated groups, the validity of findings and data withdrawal, incomplete outcome data (attrition and detection bias), and differences between data reporting or unreported data. The risk of bias assessment was presented according to the Cochrane collaboration recommendations. The overall quality of the study was graded as *'poor', 'fair'* and *'good'* based on the classification in the Cochrane's quality assessment tool.

### Statistical Analysis

All data were presented as the number of episodes of GDF in patients. Data analysis and interpretation were performed using Revman 5.3 (Revman, Version 5.3 for Windows; Copenhagen, Denmark: the Nordic Cochrane Centre, The Cochrane Collaboration, 2008) [7]. The nature of the analysis was not suitable for a pooled data analysis. Within each class of interventions (intravenous fluid and enteral feeding), a meta-analysis of GDF events was performed. Quantitative data meta-analysis was performed with at least two studies reporting on GDF as the primary or secondary outcome. Studies that did not have GDF as a primary or secondary outcome were excluded from the meta-analyses (Fig 1).

Heterogeneity was assessed by using $I^2$ and classified as < 25% - low ; 25 – 50% - moderate and > 75% as high heterogeneity (heterogeneity and subgroup analysis in Cochrane consumers and communication group reviews) [8]. Regardless of the presence or absence of heterogeneity, a random-effects model was used to provide the most conservative estimate. Pooled effects for classes of interventions were calculated as weighted mean difference (MD) with 95% confidence interval (CI). P-value < 0.05 was considered statistically significant for all analyses. Ethical approval was not necessary for a review of published trials.

## Results

### Study Selection and Characteristics

A total of 103 studies including intravenous fluids (n = 46) and enteral feeding (n = 57) were eligible for inclusion in the systematic review, of which 43 (n = 22 intravenous fluid; n = 21 enteral feeding) studies were included in the final meta-analyses.

In studies on *intravenous fluid therapy* [9-54], 46 randomised controlled trials' including 20,780 patients were systematically reviewed, of which 22 studies (n = 2696) were included in the final meta-analysis. Ten studies included mechanical ventilated critically ill patients, and the remaining 36 studies included postoperative patients. The intervention group received either restricted, goal-directed, low-infusion fluids or a controlled-expansion fluid regime given as crystalloid fluid (normal saline or plasmalyte) or colloid fluid (hydroxyethyl starch). The control group included standard, liberal, conventional, high-infusion fluids or rapid-expansion fluid regimes given as crystalloid fluids (ringers lactate, plasmalyte and saline). Five studies compared more than two groups of fluid regimes. Fifteen studies included critically ill, trauma and surgical patients with a grading of IV as per the Clavien-Dindo classification (Appendix B). The remaining studies included postoperative and acutely ill patients with Clavien-Dindo grading of II and III (Tables 1-3).

In studies on *enteral feeding* [55-111], 57 randomised controlled trials', included nearly 50% of the cohort as critically ill patients while the remaining were admitted as acute or elective surgical patients with variable admission diagnoses. The experimental group included enteral feeding delivered based on the route of feeding (enteral vs parenteral; nasogastric vs nasojejunal or jejunostomy), the timing of feeding (early vs delayed), the pattern of feeding (bolus vs continuous), or enteral feeding vs nil-by-mouth (NBM) with/without intravenous fluid. Twenty-four studies included critically ill, multiple trauma or sepsis patients with a Clavien-Dindo grading of IV. The remaining studies included postoperative and acutely ill patients with Clavien-Dindo grading of II and III (Tables 4-6).

### Quality assessment

The quality of studies was graded based on the Cochrane Quality assessment tool for randomised controlled trials for intravenous fluid (Tables 1-3) and enteral feeding (Table 4) studies (Appendix C and D). All studies met the criteria for randomisation and allocation concealment, but a wide variability existed between studies for other domains (blinding of participants and personnel, blinding of outcome assessment and assessor, incomplete outcome data and selective reporting). In the intravenous fluid group, quality assessment for 7 studies [9-15] (15%) scored *'good'* (Table 1), 11 stud-

**Table 1. Study Characteristics of 'good' quality studies on the impact of intravenous fluid therapy on gut dysfunction included in the systematic review**

| Author | Year | Study Population | Study Setting | Study type | Study patients | Admission diagnosis | Experi-mental | Intravenous fluid | Control | Intravenous fluid | Dindo-Clavien Classification* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Brandstrup[9] | 2003 | elective colorectal resection | surgery | RCT | 141 | postsurgical | 69 | restricted | 72 | standard | |
| Holte[10] | 2007 | elective surgery | surgery | RCT | 32 | elective colorectal surgery | 16 | restricted | 16 | liberal | |
| Holte[11] | 2007 | post-surgery | surgery | RCT | 48 | knee arthroplasty | 24 | restricted | 24 | liberal | |
| Gonsalez-Fajardo[12] | 2009 | post-surgery | surgery | RCT | 40 | vascular surgery transperito-neal aorto-iliac | 20 | restricted | 20 | standard | |
| Yates[13] | 2013 | elective surgery | surgery | RCT | 206 | elective colorectal surgery | 104 | starch | 98 | crystalloid | |
| Ghodraty[14] | 2017 | post-surgery | surgery | RCT | 91 | abdominal surgery | 46 | HES | 45 | ringers lactate | |
| Gómez-Izquierdo[15] | 2017 | post-surgery | surgery | RCT | 128 | colorectal surgery | 64 | GDFT | 64 | control | |

Abbreviations: HES- hydroxyethyl starch; GDFT – goal-directed fluid therapy; RCT – randomised controlled trial. * Appendix C

**Table 2. Study Characteristics of 'fair ' quality studies on the impact of intravenous fluid therapy on gut dysfunction.**

| Author | Year | Study Population | Study Setting | Study type | Study patients | Admission diagnosis | Experi-mental | Intravenous fluid | Control | Intravenous fluid | Dindo-Clavien Classification* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gan[16] | 2002 | major elective general, urologic, or gynaecologic surgery | surgery | RCT | 100 | postsurgical | 50 | GDFT | 50 | Standard | |
| Moretti [17] | 2003 | Major elective cardiac surgery | surgery | RCT | 90 | postsurgical | 30 – HetaStarch normal saline; 30 Heta Starch Balanced salt; 30 Lactated Ringers | | | | |
| Nisanevich[18] | 2005 | elective intraabdominal surgery | surgery | RCT | 157 | postsurgical | 77 | Restrictive | 75 | Liberal | |
| Kabon[19] | 2005 | open colonic resection | surgery | RCT | 253 | ICU surgical | 124 | Small volume | 129 | Large Volume | |
| Lopes[20] | 2007 | High-risk surgery | surgery | RCT | 33 | ICU surgical | 17 | GDFT | 16 | Control | |
| Vermuelen[21] | 2009 | elective major abdominal surgical procedures | surgical | RCT | 62 | surgical | 30 | Restricted | 32 | Standard | |
| Mayer[22] | 2010 | major abdominal surgery | surgery | RCT | 60 | ICU surgical | 30 | GDFT | 30 | Standard | |
| SAFE [23] | 2011 | ICU | ICU | RCT | 1218 | ICU | 603 | Colloid | 615 | Crystalloid | |
| Guidet[24] | 2012 | severe sepsis | ICU | RCT | 196 | ICU | 100 | Colloid | 96 | Crystalloid | |
| Perner[25] | 2012 | severe sepsis | ICU | RCT | 798 | ICU | 398 | Colloid | 400 | Crystalloid | |
| Reddy[26] | 2016 | critically ill | ICU | RCT | 69 | critically ill | 35 | plasmalyte | 34 | saline | |

Abbreviations: GDFT – goal-directed fluid therapy; ICU – intensive care unit; S-ICU – surgical ICU; RCT – randomised controlled trial; * Appendix C

**Table 3. Study Characteristics of 'poor ' quality studies on the impact of intravenous fluid therapy on gut dysfunction.**

| Author | Year | Study Population | Study Setting | Study type | Study patients | Admission diagnosis | Experi-mental | Intravenous fluid | Con-trol | Intravenous fluid | Dindo-Clavien Classification* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prein[27] | 1990 | post-surgery | surgery | RCT | 18 | modified Whipple's | 6- ringers' lactate ; 6 – starch ; 6- albumin | | | | I | II | III | IV |
| Salim[28] | 1991 | elective surgery | surgery | RCT | 130 | Hartmann's procedure +/- cholecystectomy | 71 | early oral | 59 | conventional intra-venous | | | | |
| Yogendran[29] | 1995 | elective surgery | surgical | RCT | 200 | surgical | 100 | Low-infusion | 100 | High infusion | | | | |
| Wilkes [30] | 2001 | elective, open surgical | surgical | RCT | 47 | surgical | 23 | Balanced | 24 | Saline | | | | |
| Lobo [31] | 2002 | post-surgery | surgery | RCT | 20 | colorectal surgery | 10 | restricted | 10 | liberal | | | | |
| Conway[32] | 2002 | major bowel surgery | surgical | RCT | 57 | surgical | 28 | GDFT | 39 | Standard | | | | |
| Venn[33] | 2002 | hip fracture surgery | surgical | RCT | 90 | surgical | 29 CON- IVF ; CVP guided FT- 31; Doppler-guided FT- 30 | | | | | | | |
| SAFE[34] | 2004 | ICU | ICU | RCT | 6997 | ICU | 3497 | Colloid | 3500 | Crystalloid | | | | |
| Parker[35] | 2004 | hip fracture surgery | surgical | RCT | 396 | surgical | 198 | Colloid | 198 | Crystalloid | | | | |
| Noblett[36] | 2005 | elective colorectal resection | surgical | RCT | 108 | surgical | 54 | GDFT | 54 | Standard | | | | |
| Wakeling[37] | 2005 | large bowel surgery | surgical | RCT | 128 | surgical | 64 | GDFT | 64 | Standard | | | | |
| Mackay[38] | 2006 | elective colorectal surgery | surgical | RCT | 80 | surgical | 41 | Restricted | 39 | Standard | | | | |
| En-quiang[38] | 2009 | critically ill | S-ICU | RCT | 76 | severe acute pancreatitis | 30 | controlled fluid expansion | 30 | rapid fluid expansion | | | | |
| Senagore[40] | 2009 | laparoscopic colectomy | surgical | RCT | 64 | surgical | 21 GDFT/LR; 21 GDFT /HS; 22 standard | | | | | | | |
| Futier[41] | 2010 | major abdominal surgery | surgery | RCT | 70 | postsurgical | 36 | Restricted-GDFT | 34 | Conservative GDFT | | | | |
| Benes[42] | 2010 | elective intraabdominal surgery | surgery | RCT | 120 | ICU surgical | 60 | GDFT | 60 | Standard | | | | |
| Pillai[43] | 2011 | post-surgery | surgery | RCT | 66 | radical cystectomy | 34 | intervention | 32 | control | | | | |
| Du[44] | 2011 | critically ill | ICU | RCT | 41 | severe acute pancreatitis | 20 | starch | 21 | ringers' lactate | | | | |
| James[45] | 2011 | Blunt and penetrating trauma | surgical | RCT | 109 | surgical | Penetrating trauma- HES 36 ; SAL 31<br>Blunt trauma- HES20 ; SAL 22 | | | | | | | |
| Challand[46] | 2012 | major elective colorectal surgery | surgical | RCT | 179 | surgical | 90 | GDFT | 89 | Standard | | | | |
| Myberg[47] | 2012 | ICU | ICU | RCT | 7000 | ICU | 3500 | Colloid | 3500 | Crystalloid | | | | |
| Srinivasa[48] | 2012 | elective colectomy | surgical | RCT | 85 | surgical | 37 | GDFT Restricted | 37 | Restricted | | | | |
| Zheng[49] | 2013 | post-surgery | surgery | RCT | 60 | gastrointestinal surgery | 30 | GDFT | 30 | control | | | | |
| Scheeren[50] | 2013 | High-risk surgery | ICU | RCT | 52 | ICU | 26 | GDFT | 26 | Control | | | | |
| Pestana[51] | 2014 | post-surgery | S-ICU | RCT | 142 | abdominal surgery | 70 | GDFT | 72 | control | | | | |
| Pearse[52] | 2014 | Major Gastrointestinal Surgery | surgery | RCT | 734 | surgical | 368 | GDFT | 366 | Standard | | | | |
| Peng[53] | 2014 | elective surgery | surgery | RCT | 80 | orthopaedic surgery | 40 | GDFT | 40 | standard | | | | |
| Reisinger[54] | 2017 | elective colorectal resection for malignancy | surgery | RCT | 58 | postsurgical | 27 | GDFT | 31 | Standard | | | | |

Abbreviations: : HES- hydroxyethyl starch ; HS- hetastach; SAL- saline; LR- lactate ringers; GDFT – goal-directed fluid therapy; ICU – intensive care unit ; S-ICU – surgical ICU; CON-IVF- conventional intravenous fluid therapy; CVP- central venous pressure; FT – fluid therapy RCT – randomised controlled trial; * Appendix C

ies [16-26] (22%) scored *'fair'* (Table 2), and more than half (63%) of the studies [27-54] were *'poor'* (Table 3). In the enteral feeding group, the majority (95%) of the studies [55-75,77-105,107-110] scored 'poor'; two studies scored *'fair'* [76, 111] and 1 study [106] was of *'good'* quality (Table 4).

### Quantitative data analysis

#### *Impact of intravenous fluid therapy on GDF*

Twenty-two randomised controlled trials [9,10,13-16,18-22,26,28,31,41-43,49,51-54] evaluated *mild to moderate* (nausea, vomiting and ileus) *and moderate to severe* (GI bleed, anastomotic leak, perforation and intestinal obstruction) GDF in 7368 patients, of which, 3682 (50%) were randomised to the intervention group (goal-directed/ restricted/ balanced intravenous fluids) and the remaining to the control group (liberal/ standard intravenous fluid). In the intervention group, no significant difference was observed for nausea, ileus, GI bleed, anastomotic leak, perforation or intestinal obstruction, in the intervention group in comparison to the control group. However, restricted/goal-directed fluid therapy in the form of colloids (starch/albumin) or a balanced fluid solution (plasmalyte /ringers lactate) was likely to reduce 'mild' GDF such as vomiting ($p = 0.03$) in critically ill and major surgical patients compared to a standard/liberal intravenous fluid regime (Table 5). Heterogeneity between studies ranged from 0 - 45 %.

#### *Impact of enteral feeding on GDF*

Twenty-one randomised controlled trials' [60,63,67,70,71-73,75,78,81,85-87,91,93,94,100,101,106,108,111] enrolled 18,543 patients of which, 50% (n = 9260) patients were randomised to the enteral nutrition groups. The remaining half (n = 9283) were randomised to the parenteral nutrition group, delayed enteral feeding or nil-by-mouth group. *Mild to moderate* GDF (vomiting, diarrhoea, abdominal distention and ileus) and *moderate to severe* (GI bleed, anastomotic leak, intestinal ischaemia, peritonitis) are presented in sub-groups (route of feeding – enteral vs. parenteral; the timing of feeding – early vs. delayed and feeding vs no feeding – enteral vs. nil-by-mouth) demonstrated in Table 6.

##### *(i) Route of feeding (enteral vs parenteral)*

In the EN group, a significant increase in vomiting episodes was observed compared to in parenteral nutrition group ($p < 0.01$). The EN group showed a trend in fewer events for anastomotic leaks ($p = 0.03$) and peritonitis ($p = 0.03$) compared to the parenteral nutrition group. Other variables of GDF, including diarrhoea, abdominal distension and intestinal ischemia, presented with no significant differences between the two groups (Table 6). Heterogeneity between studies ranged from 0 – 92 %.

##### *(ii) Timing of feeding (early vs delayed)*

Four randomised controlled trials' enrolled 324 patients, of which 50% of patients were allocated to the early enteral nutrition group and the other half to the delayed/conventional enteral nutrition group. A significant decrease in the vomiting episodes was observed in the early enteral nutrition group compared to delayed/conventional enteral nutrition group ($p < 0.01$). No differences were observed between groups for diarrhoea and abdominal distension. Heterogeneity between studies ranged from 0 – 69 %.

##### *(iii) Enteral feeding vs nil-by-mouth (NBM)*

Six randomised controlled trials' enrolled 1667 patients, of which 50% was randomised to the intervention group. There was a tendency of reduced anastomotic leaks in patients receiving enteral feeding ($p = 0.04$) compared to patients on a nil-by-mouth regimen. However, no differences were observed for events on vomiting, abdominal distension and GI bleed. (Table 6). Heterogeneity between studies ranged from 0 – 33 %.

## Discussion

The results of the meta-analysis demonstrate that restricted/goal-directed fluid therapy regardless of the type of fluid reduces mild GDF (vomiting) but not other complications associated with GDF. Enteral feeding, on the other hand, significantly increased vomiting episodes compared to parenteral nutrition but 'early' enteral nutrition significantly reduced the incidence of vomiting compared to delayed feeding. Enteral feeding was likely to reduce severe gut complications such as anastomotic leak and peritonitis compared with parenteral nutrition or an NBM status. Other mild to moderate variables of GDF (i.e. nausea, abdominal distension, ileus or diarrhoea) and moderate to severe complications (i.e. GI bleed, perforation, intestinal obstruction or intestinal ischaemia) were not associated with significant changes in outcomes. The results suggest that although the beneficial effects of restricted/goal-direct-

ed intravenous fluids and enteral feeding are essential to reduce some form of GDF, the impact is not prevalent for other variables of GDF (e.g. ileus and intestinal ischemia) associated with poor clinical outcomes. This may reflect the paucity of high-quality literature on the interaction between intravenous fluid (resuscitation) and enteral feeding as a combined therapy on the impact of GDF. The role of these two modalities in combination should be regarded as an important aspect in identifying the impact on the severity of GDF in acute surgical and critically ill patients.

*Intravenous fluid therapy* is frequently the first line of treatment in acute surgical and critically ill patients but hypervolemia and hypovolemia, both, are deemed detrimental. A revival of interest emerged almost two decades ago when hypovolemia in the form of restrictive fluid therapy was associated with improved postoperative clinical outcomes [9,16,18,31]. These studies suggested that a preferred approach of 'zero' or 'neutral' fluid balance not only improves outcomes related to gut motility but also may prevent adverse long-term outcomes. The current study demonstrated that mild GDF, i.e. vomiting, was significantly lower in patients on a restrictive/ targeted intravenous fluid regime. Studies have also reported similar results when colloids have been administered postoperatively [14,17]. The benefit of this outcome may be explained by cumulative administration of smaller volumes (of colloids) compared to crystalloids. Hypervolemia from excessive or liberal fluid administration, particularly crystalloids is associated with poor outcomes in postoperative [9,18] and in critically ill patients [25,47]. It can precipitate intestinal oedema leading to an ileus, delayed gastric emptying, feeding intolerance and hence sub-optimal nutrition delivery. Another school of thought indicates that complex surgical patients with high-risk surgeries possibly require judicious amounts of fluids to avoid complications associated with circulatory failure and gut mucosal ischemia [41,54,116,119]. This may be particularly relevant when liberal intravenous fluids are necessary to resuscitate patients after massive haemorrhagic losses for haemodynamic stability. In recent decades, goal-directed fluids have been advocated to prevent tissue hypovolemia [20] but maintain euvolemia by using targeted fluid approach raising the possibility of improved clinical outcomes in high-risk patients [22, 42, 84,121]. Hence, it is expected that a modest amount of fluids might be necessary to prevent anastomotic hypoperfusion, gut mucosal ischemia and reduce postoperative complications. Although the benefit of goal-directed fluid therapy is projected at improving organ perfusion without the onset of tissue oedema [54,117,122]; a paucity of studies exists warranting more research in this area [15, 41, 52, 118].

*Enteral Nutrition* forms an integral part of overall fluid administration in addition to intravenous fluids. Enteral nutrition and intravenous fluids combined play a crucial role in GDF outcomes, but due to a paucity of studies, this area has not received due attention. Enteral nutrition is invariably the first choice of nutrition compared to parenteral nutrition over decades [112]. The current study demonstrated that mild GDF, i.e. vomiting significantly increased in patients receiving enteral nutrition but reduced significantly when enteral feeding was commenced earlier. This is possible because 'early' enteral nutrition has multiple advantages over parenteral nutrition [75,82,114,121], and these benefits are evident in high-risk surgical and critically ill patients [70,124]. The initiation of enteral feeding is known to stimulate gut motility which reduces the incidence of GDF symptoms such as nausea and vomiting postoperatively. However, a significant difference for ileus between groups was not observed, although the number of events were lower in the enterally fed group. In cases of gut failure, when enteral feeding is contraindicated, parenteral nutrition becomes the sole choice of feeding and may be commenced within 24 hrs of ICU admission or post-surgery [120]. Administering parenteral nutrition appears to be a logical clinical decision, especially if enteral feeding raises the suspicion of non-occlusive mesenteric ischemia in the critically ill, with haemodynamic compromise. Our review showed no differences for intestinal 'ischaemia' between groups, although the events were half in the control group compared to the intervention (enteral nutrition) arm. Considering that the current review included a heterogeneous mix of patients, it is evident that in a sub-set of patients, i.e. post-cardiac surgery, severe acute pancreatitis or septic shock, administration of early enteral nutrition may potentially pose more risk than benefit by increasing the risk of bowel ischemia.

Nevertheless, the use of trophic enteral feeding has been suggested in haemodynamically unstable patients to maintain gut integrity [4]. Authors have argued that enteral nutrition comes with its risks such as aspiration, pneumonia, intestinal obstruction, necrosis and pneumonitis intestinalis. However, the present study demonstrated no such differences for any of these complications. For gastrointestinal complications, a signifi-

**Table 4. Study Characteristics of studies on the impact of enteral feeding on gut dysfunction included in the systematic review**

| Author | Year | Study Population | Study Setting | Study type | Study patients | Admission diagnosis | Experimental | Control | Dindo-Clavien Classification# | | | | Quality Grading* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | I | II | III | IV | |
| Hoover[55] | 1980 | surgical | surgical | RCT | 48 | surgical | 26 EF | 22 IVF | | | | | Poor |
| Adams[56] | 1986 | ICU surgical | ICU | RCT | 46 | multiple trauma | 23 (EN) | 23 (PN) | | | | | Poor |
| Moore[57] | 1986 | major abdo trauma | surgical | RCT | 59 | surgical | 29 (EN) | 30 (PN) | | | | | Poor |
| Bower[58] | 1986 | surgical | surgery | RCT | 20 | GI/pancreato-biliary surgery | 10 (EN-JeJ) | 10 (PN) | | | | | Poor |
| Hamoui[59] | 1989 | surgical | surgical | RCT | 19 | major GI surgery | 11 EN | 8 PN | | | | | Poor |
| Von Meyenfeldt[60] | 1992 | surgical | surgery | RCT | 101 | GI/colon cancer | 50 (EN) | 51 (PN) | | | | | Poor |
| Montecalvo[61] | 1992 | surgical | surgical | RCT | 38 | surgical | 19 NG | 19NJ | | | | | Poor |
| Dunham[62] | 1994 | critically ill | ICU | RCT | 37 | trauma | 12 (EN) + 15 (PN) + 10 (EN+PN) | | | | | | Poor |
| Borzotta[63] | 1994 | trauma | surgical trauma | RCT | 48 | trauma | 27 (EN) | 21 (PN) | | | | | Poor |
| Daly[64] | 1995 | surgical | surgical | RCT | 60 | surgical | 18 ENSD; 12 SD-IP; 19 ENSD-IP-OP; 11 EN-IP | | | | | | Poor |
| Carr[65] | 1996 | post-surgical | surgery | RCT | 28 | intestinal resection | 14 (EEN) | 14 (CEN) | | | | | Poor |
| Beier-Holgersen[66] | 1996 | post-surgical | surgery | RCT | 60 | major abdominal surgery | 30 (EEN) | 30 (placebo) | | | | | Poor |
| Baigrie[67] | 1996 | post-surgical | surgery | RCT | 97 | oesophagectomy/gastrectomy | 50 (EN) | 47 (PN) | | | | | Poor |
| VanBerge[68] | 1997 | post-surgical | surgery | RCT | 57 | pancreatoduodenectomy | 30 (CON) | 27 (CYC) | | | | | Poor |
| Kalfarentzos[69] | 1997 | critically ill | ICU | RCT | 38 | Severe acute pancreatitis | 18 (EN) | 20 (PN) | | | | | Poor |
| Heslin[70] | 1997 | surgical | surgery | RCT | 195 | upper GI malignancy | 97 (EN) | 98 (IVF) | | | | | Poor |
| Reynolds[71] | 1997 | major upper GI surgery | surgical | RCT | 67 | surgical | 33 (EN) | 34 (PN) | | | | | Poor |
| Stewart[72] | 1998 | elective surgical | surgery | RCT | 80 | colorectal resections | 40 (EOF) | 40 (COF) | | | | | Poor |
| Windsor[73] | 1998 | surgical | surgical | RCT | 34 | acute pancreatitis | 16 EN | 18PN | | | | | Poor |
| Singh[74] | 1998 | surgical | surgical | RCT | 43 | surgical | 22 JEJ | 21 IVF | | | | | Poor |
| Braga[75] | 1998 | surgical | surgical | RCT | 166 | surgical | 55 STD-EN; 55 – STD-EN enriched; 56 TPN | | | | | | Poor |
| Taylor[76] | 1999 | critically ill | ICU | RCT | 82 | head injury | 41 TRO | 41 EN | | | | | Fair |
| Pupelis[77] | 2000 | critically ill | S-ICU | RCT | 60 | severe pancreatitis/peritonitis | 30 (JEN) | 30 (Control) | | | | | Poor |
| Minard[78] | 2000 | critically ill | ICU | RCT | 27 | head injury/trauma | 12 (EEN) | 15 (DEN) | | | | | Poor |
| Powell[79] | 2000 | critically ill | ICU | RCT | 27 | severe acute pancreatitis | 13 (EN) | 14 (NBM) | | | | | Poor |
| Kearns[80] | 2000 | critically ill | ICU | RCT | 44 | critically ill | 23 G | 21 SI | | | | | Poor |
| Bozzetti[81] | 2001 | elective surgery | surgery | RCT | 317 | GI cancer | 159 (EN) | 158 (PN) | | | | | Poor |
| Braga[82] | 2001 | surgical | surgery | RCT | 257 | GI cancer | 126 (EEN) | 131 (PN) | | | | | Poor |
| Montejo[83] | 2002 | critically ill | ICU | RCT | 101 | critically ill | 50 (JEN) | 51 (GEN) | | | | | Poor |

*(Continued on next page)*

**(Table 4. Continued)**

| Author | Year | Study Population | Study Setting | Study type | Study patients | Admission diagnosis | Experimental | Control | Dindo-Clavien Classification# | | | | Quality Grading* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | I | II | III | IV | |
| Davies[84] | 2002 | critically ill | ICU | RCT | 73 | critically ill | 34 (NJ) | 39 (NG) | | | | | Poor |
| Bertolini[85] | 2003 | critically ill | ICU | RCT | 39 | Sepsis | 18(EN) | 17 (PN) | | | | | Poor |
| Kompan[86] | 2004 | critically ill | ICU | RCT | 52 | multiple trauma | 27 (EEN) | 21 (DEN) | | | | | Poor |
| Malhotra[87] | 2004 | post-surgical | surgery | RCT | 164 | perforated gut and peritonitis | 83 (EN) | 81 (NBM) | | | | | Poor |
| Kumar[88] | 2006 | Surgical | surgical | RCT | 31 | surgical | 15 NG | 16 NJ | | | | | Poor |
| Nguyen[89] | 2007 | critically ill | ICU | RCT | 31 | critically ill | 23 (NJ) | 28 (NJ) | | | | | Poor |
| Han-Guerts[90] | 2007 | post-surgical | surgery | RCT | 150 | oesophagectomy | 71 (ND) | 79 (JEJ) | | | | | Poor |
| Descahy[91] | 2008 | critically ill | ICU | RCT | 100 | ICU | 50 EEN | 50 CEN | | | | | Poor |
| Tien[92] | 2009 | critically ill | ICU | RCT | 200 | ICU | 98 TRO | 102 EN | | | | | Poor |
| Barlow[93] | 2011 | Surgical | surgery | RCT | 121 | upper GI malignancy | 64 (EN) | 57 (NBM+IVF) | | | | | Poor |
| Altintas[94] | 2011 | critically ill | ICU | RCT | 71 | ICU | 30 (EN) | 41 (PN) | | | | | Poor |
| Rice[95] | 2011 | Surgical | surgical | RCT | 247 | surgical | EN 123 | 124 IVF | | | | | Poor |
| Davies[96] | 2013 | critically ill | ICU | RCT | 181 | ICU | 91 NJ | 89 NG | | | | | Poor |
| Zhu[97] | 2013 | post-surgical | surgery | RCT | 68 | pancreaticoduodenectomy | 34(JT) | 34 (NJT) | | | | | Poor |
| Sun[98] | 2013 | critically ill | S-ICU | RCT | 60 | severe acute pancreatitis | 30 (EEN) | 30 (DEN) | | | | | Poor |
| Kadamani[99] | 2014 | critically ill | ICU | RCT# | 15 | critically ill | 15 (CON) | 15 (BOL) | | | | | Poor |
| Boelens[100] | 2014 | elective surgical | surgery | RCT | 123 | rectal surgery | 61 (EEN) | 62 (EPN) | | | | | Poor |
| Harvey[101] | 2014 | critically ill | ICU | RCT | 2388 | critically ill | 1197 (EN) | 1191(PN) | | | | | Poor |
| Ma[102] | 2015 | acute surgical | surgery | RCT | 35 | acute pancreatitis | 17 (NTF) | 18 (NPO) | | | | | Poor |
| Bing Li[103] | 2015 | post-surgical | surgery | RCT | 400 | gastrectomy | 200 (EEN) | 200 (PN) | | | | | Poor |
| Taylor[104] | 2016 | critically ill | ICU | RCT | 50 | critically ill | 25 (NJ) | 25 (NG + ProK) | | | | | Poor |
| Ozen[105] | 2016 | critically ill | ICU | RCT | 51 | critically ill | 26 (no-GRV's) | 25 (GRV's) | | | | | Poor |
| Van Barneveld[106] | 2016 | elective surgical | surgery | RCT | 123 | rectal ca malignancy | 61 (EEN) | 62 (EPN) | | | | | Good |
| Malik[107] | 2016 | critically ill | ICU | RCT | 60 | critically ill | 30 (EF) | 30 (placebo) | | | | | Poor |
| Fan[108] | 2016 | critically ill | ICU | RCT | 80 | Severe TBI | 40 (EN) | 40 (PN) | | | | | Poor |
| Stimac[109] | 2016 | acute pancreatitis | pancre-atitis | RCT | 214 | acute pancreatitis | 107 EN | 107 IVF | | | | | Poor |
| Hongyin[110] | 2017 | acute surgical | surgery | RCT | 161 | acute pancreatitis | 83 (APD)/61 EN) | 78(non-APD)/68(EN) | | | | | Poor |
| Reigner[111] | 2018 | critically ill | ICU | RCT | 2410 | shock | 1202 (EN) | 1208 (PN) | | | | | Fair |

*Abbreviations : EEN – early enteral feeding; CEN – conventional enteral feeding; EN – enteral nutrition; PN parenteral nutrition; CON – continuous enteral feeding; CYC – cyclic enteral feeding; EOF – early oral feeding ; COF – conventional oral feeding ;JEN – jejunal enteral nutrition; DEN – delayed enteral nutrition ; NBM – nil by mouth; GEN – gastric enteral nutrition ; NJ – nasojejunal; NG nasogastric; ND – nasoduodenal; JEJ- jejunostomy ; JT – jejeunostomy tube ; NJT – nasojejunal tube; BOL – bolus ; EPN – early parenteral nutrition; NTF – nasogastric tube feeding; NPO – nil per oral; ProK – prokinetics; GRV – gastric residual volumes; APD – abdominal paracentesis drainage ;ICU – intensive care unit ; S-ICU – surgical ICU; RCT – randomised controlled trial, # - pseudo-RCT; GI – gastrointestinal; TBI – traumatic brain injury; IVF – intravenous fluids; TRO- trophic feeding; ENSD – enteral nutrition with supplemented diet; IP inpatient; OP – outpatient; STD – standard;# D-C classification Appendix C; * Thresholds for Converting the Cochrane Risk of Bias Tool.*

**Table 5. Impact of intravenous fluid therapy on variables of gut dysfunction**

| Symptoms of GDF § | Intervention[a] | Control | Odds Ratio [95% CI]* | P Trend | I² (%)# |
|---|---|---|---|---|---|
| Nausea | 88/ 274 | 90/278 | 0.98 (0.67, 1.44) | 0.92 | 0 |
| Vomiting | 62/462 | 94/447 | 0.51 (0.28, 0.94) | **0.03** | 45 |
| Ileus | 66/832 | 80/828 | 0.83 (0.52, 1.32) | 0.42 | 23 |
| GI bleed | 15/592 | 10/587 | 1.48 (0.66, 3.35) | 0.34 | 0 |
| Anastomotic leak | 44/833 | 43/867 | 1.03 (0.54, 1.96) | 0.93 | 31 |
| Perforation | 7/238 | 6/234 | 1.05 (0.36, 3.09) | 0.92 | 0 |
| Intestinal obstruction | 5/451 | 11/445 | 0.53 (0.20, 1.45) | 0.22 | 0 |

a: restricted, goal-directed, low-infusions or a controlled-expansion fluid therapy given as crystalloid fluid (normal saline or plasmalyte) or colloid fluid (hydroxyethyl starch)
b: standard, liberal, conventional, high-infusions or rapid-expansion fluid regimes given as crystalloid fluids (ringers lactate, plasmalyte and saline).
*CI - Confidence interval used; Significant P values (<0.05) are shown in bold; #I2 - heterogeneity between studies expressed as percentages; **§** GDF - gut dysfunction

**Table 6. Impact of enteral feeding on variables of gut dysfunction as classified by feeding categories**

| Symptoms of GDF§ | Intervention Enteral | Control Parenteral | Odds Ratio [95% CI]* | P Trend | I² [%]# |
|---|---|---|---|---|---|
| **A. Route of feeding** | | | | | |
| Vomiting | 605/2388 | 350/2598 | 2.02 (1.74, 2.35) | **<0.01** | 0 |
| Diarrhoea | 190/1508 | 421/1515 | 1.75 (0.39, 7.86) | 0.46 | 92 |
| Abdominal distension | 123/1386 | 90/1390 | 1.51 (0.93, 2.45) | 0.10 | 28 |
| Ileus | 52/347 | 65/347 | 0.97 (0.34, 2.76) | 0.96 | 58 |
| Anastomotic leak | 28/540 | 54/545 | 0.54 (0.31, 0.95) | **0.03** | 14 |
| Intestinal ischaemia | 33/2493 | 16/2495 | 1.87 (0.72, 4.87) | 0.20 | 42 |
| Peritonitis | 5/265 | 18/268 | 0.31 (0.11, 0.87) | **0.03** | 0 |
| **B. Timing of feeding** | Early | Delayed | | | |
| Vomiting | 3/56 | 19/54 | 0.11 (0.03, 0.41) | **<0.01** | 0 |
| Diarrhoea | 27/39 | 23/40 | 2.45 (0.26, 22.75) | 0.43 | 69 |
| Abdominal Distension | 12/66 | 21/69 | 0.51 (0.22, 1.91) | 0.12 | 0 |
| **C. Enteral feeding vs Nil-by-mouth (NBM)** | Enteral | NBM | | | |
| Vomiting | 21/220 | 22/219 | 0.72 (0.18, 2.90) | 0.65 | 0 |
| Abdominal Distension | 66/242 | 48/240 | 1.40 (0.75, 2.64) | 0.29 | 33 |
| GI bleed | 2/133 | 2/133 | 0.99 (0.17, 5.86) | 0.99 | 0 |
| Anastomotic leak | 12/244 | 24/236 | 0.46 (0.22, 0.95) | **0.04** | 0 |

*CI - Confidence interval used; Significant P values (<0.05) are shown in bold; #I2 - heterogeneity between studies expressed as percentages; **§** GDF - gut dysfunction

cant reduction in anastomotic leaks in the enteral nutrition group suggesting its benefits irrespective of the feeding route was observed. It is common practice in some areas, particularly intensive care, to commence patients on parenteral nutrition with anastomotic leaks before a trial of enteral nutrition. However, it should be acknowledged that a correct assessment for an enteral nutrition challenge can be countered in patients on parenteral nutrition with significant complications (e.g. anastomotic leaks), hence lowering the threshold of initiating enteral nutrition. Barlow et al. [93] found a lower incidence (2 vs 7) of anastomotic leaks in the early enteral nutrition group. They attributed a three-day shorter length of stay and reduced postoperative complications from installing early enteral nutrition. A similar effect was confirmed by a Cochrane review [115] in which enteral nutrition reduced the risk of anastomotic leaks from 27% in the standard group to 13% in early enteral group. These results affirmed with the present findings. It is hypothesised that enteral nutrition may improve perfusion at the anastomosis site, which promotes mucosal wound healing and prevents further leaks.

In comparison, Lewis et al. (2009) did not support this finding and observed mortality of 50% in the intervention group (enteral group) with anastomotic leaks [114]. However, it is likely that a smaller sample

size may result in a false positive rate for mortality, thus exaggerating the magnitude of the negative result. The benefit of enteral feeding in complications such as perforation and peritonitis has been confirmed by several reports, which resonated with our findings. Early enteral feeding seems to maintain gut integrity by improving mucosal circulation and oxygen delivery that may reduce the risk of peritonitis [74, 87,113].

The present study is not without limitations:

1. The severity score in majority of the studies including surgical patients was low (ranging between I to III) hence the overall effect may be confounded by the clinical severity of the cohort. The majority of studies were conducted in stable postoperative patients and results may not be generalisable to a high-risk group, e.g. septic shock.

2. Critically ill patients are a heterogeneous group, and the effect on gut function can differ with specific sub-population. Such high-risk heterogenous patients need to be assessed in robust, well-designed, and randomised controlled trials. A possible stumbling block may be the ethical dilemma of implementing clinical trials using regimented interventions in these patients is often challenging for institutions and ethics committees.

3. Individualised unit protocols were variable with prescription of fluid and enteral feeding regimes possibly confounding the overall impact on GDF outcomes.

4. Most studies included small numbers of patients and were single-centred studies.

5. Postoperative morbidity manifested as GDF may be associated with the type of surgical procedure or manipulation of the bowel during surgery which may be associated with inducing a surgical stress response. However, this is expected to be low in our study, considering that the majority of the cohort included stable postoperative patients.

6. The majority of our studies found no differences between long-term endpoints (mortality and length of stay) but the occurrence of GDF was excluded from primary endpoints.

7. Most importantly, it was difficult to define or classify gut dysfunction because, until now, there is no valid, objective or a reliable scoring system to assess gut function in intensive care patients [125]. This suggests the need to develop a novel scoring tool to address this concern in future trials. Due to fewer studies on the effect of intravenous fluids and enteral nutrition on GDF, our meta-analyses may have been underpowered to see significant outcomes on GDF. Overall, studies on intravenous fluid remain mostly inconclusive, and potentially the impact of intravenous fluids may project variable outcomes when applied to a homogenous cohort instead of heterogeneous patient groups.

Further, inconclusive results from large-scale fluid and enteral feeding trials raise the suspicion that GDF may be the missing link, which perhaps may be associated with long-term outcomes. This dimension is often ignored when evaluating endpoints. To observe a difference in the key outcome, we first need to understand the combined effects of intravenous fluids and enteral nutrition in influencing clinical outcomes, including GDF. It is expected that as a result of the potential interaction between these two modalities, patients receiving liberal fluid resuscitation and early aggressive feeding are more likely to be at risk of severe GDF. More work is required to understand the implications of intravenous fluids and enteral nutrition on GDF and how this may impact overall patient outcomes. Future studies should evaluate this potential interaction and assess the combined impact of these two modalities on GDF in surgical and critically ill patients.

## Conclusion

A restricted/goal-directed fluid regime and early enteral feeding compared to parenteral or a nil-by-mouth regime may reduce the risk on mild GDF in some, but not all complications of severe GDF. Because of a preventive strategy, we need to first understand the interaction between both (intravenous fluids and enteral feeding) and their impact on the gut so its implications can be translated into clinical practice eventually. Hence, it can be hypothesised that conservative fluid resuscitation and aggressive enteral feeding may potentially be the fundamental cause of developing severe life-threatening GDF (i.e. intestinal ischemia) and complications that can delay recovery and affect clinical outcomes in acute surgical and critically ill patients. Future research should evaluate and focus on an extended conceptual framework on the cross-interaction of conservative and aggressive modes across these two interventions and its impact on various levels of severity of GDF.

## Author contributions

V Asrani and JA Windsor contributed to the conception and design of the research. V Asrani performed the literature search, extracted, analysed and interpreted

data, and drafted the manuscript. A Brown contributed to the literature search, data acquisition and analysis, and co-reviewed the data. JA Windsor and I Bissett critically revised the manuscript and supervised the project. All authors read and approved the final version of the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the manuscript.

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## Declaration of Conflicting Interests

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**Appendix A : Search Strategy**

| # Searches Results |
|---|
| 1 Gastrointestinal Diseases/ |
| 2 ((gastrointestinal or intestin* or digestive) adj3 (dysfunction* or failure or disorder* or injur* or disease*)).mp. |
| 3 ((abdominal or gut or bowel or intestin*) adj3 (perforat* or infarct* or obstruct* or failure or ischemi*)).mp. |
| 4 gastroparesis.mp. or Gastroparesis/ |
| 5 gastrointestinal motilit*.mp. or exp Gastrointestinal Motility/ |
| 6 (dysmotilit* or intestinal motilit*).mp. 5645 |
| 7 Intra-Abdominal Hypertension/ |
| 8 (abdominal compartment syndrome* or intra abdominal hypertension or intraabdominal hypertension).mp. |
| 9 feed* intolerance.mp. |
| 10 ileus.mp. or Ileus/ |
| 11 Intestinal Obstruction/ or Intestinal Pseudo-Obstruction/ or pseudo obstruction.mp. or ogilvie's syndrome.mp. |
| 12 (mesenteric or peritonitis).mp. 91360 |
| 13 or/1-12 282880 |
| 14 enteral nutrition/ or parenteral nutrition/ |
| 15 Parenteral Nutrition, Total/ |
| 16 ((enteral or parenteral) adj3 (feed* or nutrition)).mp. |
| 17 Fluid Therapy/ or intravenous fluid*.mp. |
| 18 (fluid* adj3 therap*).mp. |
| 19 (resuscitation adj3 fluid*).mp. |
| 20 vasoactive.mp. |
| 21 Vasoconstrictor Agents/ or vasoconstrictor*.mp. or vasopressor*.mp. |
| 22 inotrope*.mp. |
| 23 or/14-22 |
| 24 intensive care/ or critical illness/ |
| 25 Intensive Care Units/ |
| 26 General Surgery/ |
| 27 Postoperative Complications/ or Postoperative Care/ |
| 28 (intensive care or ICU or critical care or critical* ill*).mp. |
| 29 (surgery or surgical or postoperative).mp. |
| 30 or/24-29 |
| 31 randomized controlled trial.pt. |
| 32 controlled clinical trial.pt. |
| 33 randomized.ab. |
| 34 placebo.ab. 35 drug therapy.fs. |
| 36 randomly.ab. |
| 37 trial.ab. 38 groups.ab. |
| 39 or/31-38 |
| 40 adult/ or aged/ or "aged, 80 and over"/ or frail elderly/ or middle aged/ or (adult* or middle aged or older or old or aged or elderly or geriatric* or frail).mp. |
| 41 13 and 23 and 30 and 39 and 40 |
| 42 exp animals/ not humans.sh |
| 43 41 not 42 |

**Appendix B. Dindo-Clavien Classification**

| Grade | Grade Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications, Blood transfusions and total parenteral nutrition are also included |
| Grade III | Requiring surgical, endoscopic or radiological intervention<br>Grade IIIa Intervention not under general anaesthesia<br>Grade IIIb Intervention under general anaesthesia |
| Grade IV | Life-threatening complication (including CNS complications)* requiring IC/ICU management<br>Grade IVa Single organ dysfunction (including dialysis)<br>Grade IVb Multiorgan dysfunction) |

Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications: A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. Annals of Surgery. 2004; 240 (2): 205-213.

**Appendix C. Quality assessment for studies on the effect of intravenous fluid therapy on gut dysfunction (Cochrane quality grading for randomised controlled trials)[7]**

| Author | Year | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Blinding of outcome assessor | Incomplete outcome data | Selective outcome reporting? | Quality Grading |
|---|---|---|---|---|---|---|---|---|---|
| Prein | 1990 | | | | | | | | Poor |
| Salim | 1991 | | | | | | | | Poor |
| Yogendran | 1995 | | | | | | | | Poor |
| Wilkes | 2001 | | | | | | | | Poor |
| Lobo | 2002 | | | | | | | | Poor |
| Gan | 2002 | | | | | | | | Fair |
| Conway | 2002 | | | | | | | | Poor |
| Venn | 2002 | | | | | | | | Poor |
| Moretti | 2003 | | | | | | | | Fair |
| Brandstrup | 2003 | | | | | | | | Good |
| SAFE | 2004 | | | | | | | | Poor |
| Parker | 2004 | | | | | | | | Poor |
| Nisanevich | 2005 | | | | | | | | Fair |
| Kabon | 2005 | | | | | | | | Fair |
| Noblett | 2005 | | | | | | | | Poor |
| Wakeling | 2005 | | | | | | | | Poor |
| Mackay | 2006 | | | | | | | | Poor |
| Holte | 2007 | | | | | | | | Good |
| Holte | 2007 | | | | | | | | Good |
| Lopes | 2007 | | | | | | | | Fair |
| Golsalez-Fajardo | 2009 | | | | | | | | Good |
| Mao | 2009 | | | | | | | | Poor |
| Vermuelen | 2009 | | | | | | | | Fair |
| Senagore | 2009 | | | | | | | | Poor |
| Futier | 2010 | | | | | | | | Poor |
| Benes | 2010 | | | | | | | | Poor |
| Meyer | 2010 | | | | | | | | Fair |
| Pillai | 2011 | | | | | | | | Poor |
| Du | 2011 | | | | | | | | Poor |
| James (FIRST) | 2011 | | | | | | | | Poor |
| SAFE 2011 | 2011 | | | | | | | | Fair |
| Challand | 2012 | | | | | | | | Poor |
| Myberg | 2012 | | | | | | | | Poor |
| Srinivasa | 2012 | | | | | | | | Poor |
| CRYSTMAS | 2012 | | | | | | | | Fair |
| Perner | 2012 | | | | | | | | Fair |
| Yates | 2013 | | | | | | | | Good |
| Zheng | 2013 | | | | | | | | Poor |
| Scheeren | 2013 | | | | | | | | Poor |
| Pestana | 2014 | | | | | | | | Poor |
| Peng | 2014 | | | | | | | | Poor |
| Pearse | 2014 | | | | | | | | Poor |
| Reddy | 2016 | | | | | | | | Fair |
| Ghodraty | 2017 | | | | | | | | Good |
| Gómez-Izquierdo | 2017 | | | | | | | | Good |
| Reisinger | 2017 | | | | | | | | Poor |

*Thresholds for Converting the Cochrane Risk of Bias Tool: Good quality: All criteria met (i.e. low for each domain); Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results Poor quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are significant limitations that could invalidate the results OR Two or more criteria listed as high or unclear risk of bias

**Appendix D. Quality assessment for studies on the effect of enteral feeding on gut dysfunction (Cochrane quality grading for randomised controlled trials)[7]**

| Author | Year | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Blinding of outcome assessor | Incomplete outcome data | Selective reporting bias | Quality grading |
|---|---|---|---|---|---|---|---|---|---|
| Hoover | 1980 | | | | | | | | Poor |
| Adams | 1986 | | | | | | | | Poor |
| Moore | 1986 | | | | | | | | Poor |
| Bower | 1986 | | | | | | | | Poor |
| Hamoui | 1989 | | | | | | | | Poor |
| Von Meyenfeldt | 1992 | | | | | | | | Poor |
| Montecalvo | 1992 | | | | | | | | Poor |
| Dunham | 1994 | | | | | | | | Poor |
| Borzotto | 1994 | | | | | | | | Poor |
| Daly | 1995 | | | | | | | | Poor |
| Baigrie | 1996 | | | | | | | | Poor |
| Beier-Holgersen | 1996 | | | | | | | | Poor |
| Carr | 1996 | | | | | | | | Poor |
| VanBerge | 1997 | | | | | | | | Poor |
| Kalfarentzos | 1997 | | | | | | | | Poor |
| Heslin | 1997 | | | | | | | | Poor |
| Reynolds | 1997 | | | | | | | | Poor |
| Stewart | 1998 | | | | | | | | Poor |
| Windsor | 1998 | | | | | | | | Poor |
| Singh | 1998 | | | | | | | | Poor |
| Braga | 1998 | | | | | | | | Poor |
| Taylor | 1999 | | | | | | | | Poor |
| Minard | 2000 | | | | | | | | Poor |
| Powell | 2000 | | | | | | | | Poor |
| Pupelis | 2000 | | | | | | | | Poor |
| Kearns | 2000 | | | | | | | | Poor |
| Bozzetti | 2001 | | | | | | | | Poor |
| Braga | 2001 | | | | | | | | Poor |
| Davies | 2002 | | | | | | | | Poor |
| Montejo | 2002 | | | | | | | | Poor |
| Bertolini | 2003 | | | | | | | | Poor |
| Kompan | 2004 | | | | | | | | Poor |
| Kumar | 2006 | | | | | | | | Poor |
| Han-Guerts | 2007 | | | | | | | | Poor |
| Nguyen | 2007 | | | | | | | | Poor |
| Descahy | 2008 | | | | | | | | Poor |
| Tien | 2009 | | | | | | | | Poor |
| Barlow | 2011 | | | | | | | | Poor |
| Rice | 2011 | | | | | | | | Poor |
| Altintas | 2011 | | | | | | | | Poor |
| Davies | 2012 | | | | | | | | Poor |
| Sun | 2013 | | | | | | | | Poor |
| Zhu | 2013 | | | | | | | | Poor |
| Boelens | 2014 | | | | | | | | Poor |
| Kadamani | 2014 | | | | | | | | Poor |
| Harvey | 2014 | | | | | | | | Poor |
| Bing Li | 2015 | | | | | | | | Poor |
| Ma | 2015 | | | | | | | | Poor |
| Malik | 2016 | | | | | | | | Poor |
| Ozen | 2016 | | | | | | | | Poor |
| Taylor | 2016 | | | | | | | | Fair |
| Van Barneveld | 2016 | | | | | | | | Good |
| Fan | 2016 | | | | | | | | Poor |
| Stimac | 2016 | | | | | | | | Poor |
| Hongyun | 2017 | | | | | | | | Poor |
| Reigner | 2018 | | | | | | | | Fair |

*Thresholds for Converting the Cochrane Risk of Bias Tool: Good quality: All criteria met (i.e. low for each domain); Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known significant limitation that could invalidate the results; Poor quality: One criterion not met (i.e. high risk of bias; for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are significant limitations that could invalidate the results OR Two or more criteria listed as high or unclear risk of bias