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Review

Postoperative ileus: Recent developments in pathophysiology and management☆

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SUMMARY

Background & aims: Postoperative ileus (POI) is a frequent occurrence after abdominal and other types of surgery, and is associated with significant morbidity and costs to health care providers. The aims of this narrative review were to provide an update of classification systems, preventive techniques, pathophysiological mechanisms, and treatment options for established POI.
Methods: The Web of Science, MEDLINE, PubMed and Google Scholar databases were searched using the key phrases 'ileus', 'postoperative ileus' and 'definition', for relevant studies published in English from January 1997 to August 2014.
Results: POI is still a problematic and frequent complication of surgery. Fluid overload, exogenous opioids, neurohormonal dysfunction, and gastrointestinal stretch and inflammation are key mechanisms in the pathophysiology of POI. Evidence is supportive of thoracic epidural analgesia, avoidance of salt and water overload, alvimopan and gum chewing as measures for the prevention of POI, and should be incorporated into perioperative care protocols. Minimal access surgery and avoidance of nasogastric tubes may also help. Novel strategies are emerging, but further studies are required for the treatment of prolonged POI, where evidence is still lacking.
Conclusions: Although POI is often inevitable, methods to reduce its duration and facilitate recovery of postoperative gastrointestinal function are evolving rapidly. Utilisation of standardised diagnostic classification systems will help improve applicability of future studies.

1. Introduction

The word ileus comes from the Greek 'ειλεός (eileos)' meaning a rolling or twisting, and is often given to conditions affecting the small intestine, whilst the word colic is derived from 'κωλικός (kolikos)' - belonging to the colon. In the extant works of Aurelius Cornelius Celsus, 'eileos' was identified as causing pain above the umbilicus, vomiting and more acute symptoms. 'Kolikos' pertained to conditions of the large intestine, absence of flatus, and a more protracted illness. Incisions were made in the abdomen at the level of the perceived 'evil', and barley groats, oil and honey applied. Gradual reintroduction of diet (including wine) was permitted as the patient's condition improved [1].

Historically, the term ileus has been used to describe failure of gastrointestinal peristalsis for both mechanical and non-mechanical causes. The modern usage reflects a state of absence or reduced peristalsis that can be attributed to a 'normal', prolonged, or a pathological response of the gastrointestinal tract. This failure of peristalsis results in accumulation of gastrointestinal secretions, leading to abdominal distension and vomiting. Prolonged ileus may necessitate parenteral nutrition [2].

Postoperative ileus (POI) is a common occurrence following gastrointestinal and other types of surgery (including orthopaedic, gynaecological and urological surgery) [3–6], leading to increased patient morbidity, hospital costs [7–9], and 30-day readmission rates [10].

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List of abbreviations

CI	Confidence interval
COX	Cyclo-oxygenase
EA	Epidural analgesia
ERP	Enhanced recovery programme
HR	Hazard ratio
IL	Interleukin
LOS	Length of stay
MLC	Myosin light chain
NGT	Nasogastric tube
NHE	Sodium–hydrogen exchanger
POI	Postoperative ileus
RCT	Randomised controlled trial
SBO	Small bowel obstruction
STAT	Signal transducer and activator of transcription
TNF	Tumour necrosis factor
VIP	Vasoactive intestinal polypeptide
WMD	Weighted mean difference

The aims of this narrative review were to describe the pathophysiological changes leading to POI and to assess the efficacy of interventions designed to prevent and treat POI.

2. Methods

The Web of Science, Medline, PubMed and Google Scholar databases were searched using the key phrases 'ileus' and 'postoperative ileus', for relevant studies published in English from January 1997 to August 2014. Large cohort studies, randomised controlled trials and meta-analyses were sought, along with mechanistic human and animal studies; other studies were used when these were not available. Abstracts, case reports and papers published in languages other than English were excluded. Studies related to pseudo-obstruction and delayed gastric emptying after pancreatic surgery were also excluded. The bibliographies of extracted papers were also searched manually for relevant articles. References preceding the search period were included if there were no recent studies that addressed the issue.

3. Definitions and classification

The physiological stress response appears to mandate a short period of intestinal paralysis and the return of gastrointestinal function after surgery occurs in stages: the small bowel recovers between 0 and 24 h, the stomach between 24 and 48 h and the colon between 48 and 72 h [11].

The difficulty lies in defining what is currently accepted, utilising current best practice, as a 'normal' duration of intestinal paralysis, and when this is prolonged. Durations of anywhere from 1 to 7 days have been proposed when defining prolonged POI [2]. Two studies have brought some clarity and have helped in the classification of POI. A systematic review and a global online survey of clinical researchers were conducted by Vather et al. [2]. The findings [2] closely agreed with those published by the Postoperative Ileus Management Council in 2006 [12].

Practical definitions of POI [2,12] along with a classification according to the location within the gut affected [12] are listed in Table 1.

4. Epidemiology

Although ileus is a common occurrence following surgery, it can occur with other conditions, such as sepsis. One study identified ileus as occurring in 17% of patients following colectomy, leading to a 29% increase in hospital length of stay (LOS), and a 15% increase in hospital costs [13]. A retrospective analysis examined the cost of POI in 186 patients undergoing colectomy. Overall, 24% of patients developed a POI, yet these accounted for 35% of the total expenditure of the whole cohort [14]. A larger study conducted across 160 US hospitals found that POI occurred after up to 19% of abdominal operations, leading to a prolonged mean LOS (11.5 d *vs*. 5.5 d) and costing substantially more ($18,877 *vs*. $9460) per case. The total estimated annual cost of POI to the US health economy is $1.46 billion [7].

5. Risk factors

Risk factors and possible mechanisms for POI are summarised in Table 2 [15–24].

6. Clinical features and diagnostic criteria

Failure of peristalsis results in the accumulation of gastrointestinal secretions within the lumen of the gut. This manifests as abdominal pain, symmetrical abdominal distension, anorexia, nausea or vomiting, and failure to pass stool or flatus. Prolonged POI may necessitate parenteral nutrition. A degree of ileus can be expected in the early postoperative phase, particularly in the emergency setting: peritonitis, pre-existing electrolyte disturbances, a prolonged operative duration, significant bowel handling and excessive blood loss put patients at risk of primary and secondary causes of POI [15,17,21,25]. The clinical presentation of POI overlaps with that of early postoperative small bowel obstruction and it is essential to differentiate between the two. A prolonged or recurrent POI should prompt the clinician to investigate further, especially in the presence of other factors, such as sepsis. Computed tomography (Fig. 1) can identify evidence of mechanical obstruction as a transition point where the calibre of the bowel tapers, or evidence of secondary causes, such as intra-abdominal abscess or anastomotic leak, and is the accepted investigation [13,25].

7. Complications

Accumulated secretions in the gastrointestinal tract can manifest with vomiting, which can lead to pulmonary aspiration. Ineffective peristalsis causes impaired fluid, electrolyte and nutrient

Table 1
Definitions and sub-classification of postoperative ileus [2,12].

Definitions [2,12]
POI is a transient cessation of coordinated bowel motility after surgical intervention which prevents effective transit of intestinal contents or tolerance of oral intake.
Recurrent POI is the occurrence of ileus after an apparent resolution of the immediate postoperative POI.
A primary POI occurs in the absence of any precipitating cause, and a secondary POI occurs in the presence of a complication (e.g. sepsis, anastomotic leak).
Prolonged POI • >3 days for laparoscopic surgery • >5 days for open surgery

Sub-classification [12]

Type	Definition
1	Affects the entire gastrointestinal tract with nausea, vomiting, and a failure to pass flatus or stool.
2	Affects the upper gastrointestinal tract with nausea and vomiting, but with the presence of colonic activity.
3	Manifests as no passage of flatus and/or stool, but with tolerance of diet.

Table 2
Risk factors for postoperative ileus.

Risk factor	Possible mechanisms
Increasing age [22,24].	Reduced overall capacity for the body to recover from surgical insult [24].
Male gender [17].	Increased inflammatory response to surgery [19].
	Increased pain threshold in males [16], resulting in higher catecholamine release [20].
Low preoperative albumin [24].	Increased oedema and stretch of gut
Acute and chronic opioid use [15,22].	μ-opioid receptor stimulation ameliorates peristalsis [18,23].
Previous abdominal surgery [22].	Increased need for adhesiolysis, increased bowel handling
Pre-existing airways/peripheral vascular disease [17].	Reduced physiological reserve
Long duration of surgery [15,17].	Increased bowel handling [21] and opiate use
Emergency surgery[16,19]	Increased inflammatory and catecholamine response; secondary causes of POI
Blood loss and need for transfusion [15,17,22,24].	Increased crystalloid administration resulting in oedema
Procedures requiring stomas [19].	Oedema in abdominal wall muscle and cut bowel

reabsorption, fluid and electrolyte imbalance and nutritional deficiencies. This can lead to a compromised immune system [26] putting patients at risk of sepsis. Patients who develop a prolonged POI are at higher risk of deep vein thrombosis [22], suffer more pain and discomfort, have decreased mobility, and dissatisfaction with the surgical outcome [27].

8. Pathophysiological mechanisms

A complex interplay between neurogenic, inflammatory, humoural, fluid and electrolyte, and pharmacologic components play a role in the development of POI (Fig. 2) [28–32].

Peristalsis is closely dependent upon parasympathetic stimulation, and is inhibited by sympathetic stimulation. The first phase of reaction to surgery is mediated neurally, and involves neural reflexes activated during and immediately after surgery. Incision of the skin induces an increase in adrenergic motor neuronal activity, mediated by corticotrophin releasing factor, leading to an acute intestinal paralysis [31]. However, other factors, including non-adrenergic pathways, play a role in the arrest of peristalsis [32]. Modulation of the response of the bowel to adrenergic stimulation using beta blockers has not demonstrated any conclusive benefit [33].

The second phase begins 3–4 h after surgical manipulation, and is mediated through inflammation. Release of pro-inflammatory cytokines and chemokines causes up-regulation of intracellular adhesion molecules in the endothelium [34]. Phagocytes residing throughout the gut are activated, resulting in a migration of leucocytes to the *muscularis externa*. The release of nitric oxide and prostaglandins by these phagocytes prevents peristalsis by inhibiting smooth muscle contractility directly. Modulation of vagal afferents has been suggested as a method of attenuating this inflammatory response, since release of acetylcholine can reduce cytokine release by intestinal macrophages [35].

Bowel handling appears to cause an increase in gastrointestinal inflammation, leading to an increase in the duration of POI [21]. Whilst bowel handling cannot be obviated completely, minimal access techniques using laparoscopy appear to reduce the magnitude of the systemic inflammatory response [36], and the duration of POI [37].

Potassium facilitates depolarisation of smooth muscle cell membranes, causing voltage dependent calcium channels to open, leading to an influx of extracellular calcium and subsequent smooth muscle contraction. Hypokalaemia is believed to cause ileus, but the evidence for this association derives from observational studies alone: a case series of 18 patients published in 1970 observed that hypokalaemia occurred during ileus, which subsequently resolved following correction of hypokalaemia [38]. A more recent cohort study also identified this association [22].

Fluid overload following elective surgery is associated with an increased time until first passage of flatus and stool, prolonged gastric emptying time, and increased time to tolerance of solid food [39]. Invasive monitoring is advocated to guide intraoperative fluid administration [40], and prevent fluid overload. Oedema is now understood to cause intestinal stretch, stimulating an interaction between intracellular messengers. At the molecular signalling level, signal transduction and activator of transcription-3 and NF-kB, which are important mediators involved in smooth muscle activity in the gut, affect the level of transcription of inducible nitric oxide synthase - a mediator of smooth muscle relaxation [29].

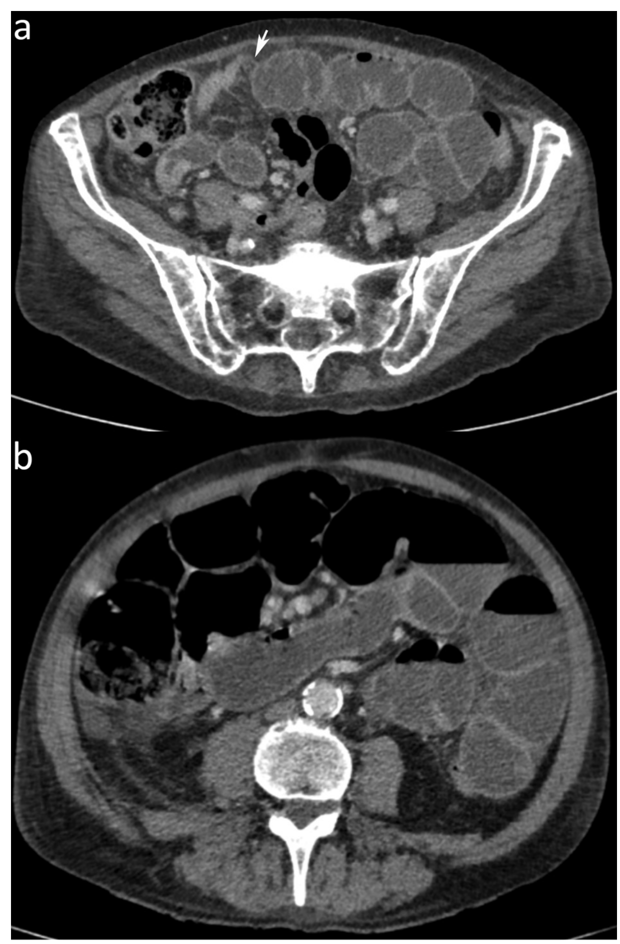

Fig. 1. a) Abdominal CT scan in a patient with small bowel obstruction demonstrating transition (arrow) between dilated small bowel proximal to the obstruction and collapsed bowel distally. b) Abdominal CT scan in a patient with postoperative ileus demonstrating fluid and air filled dilated bowel loops without a transition point.

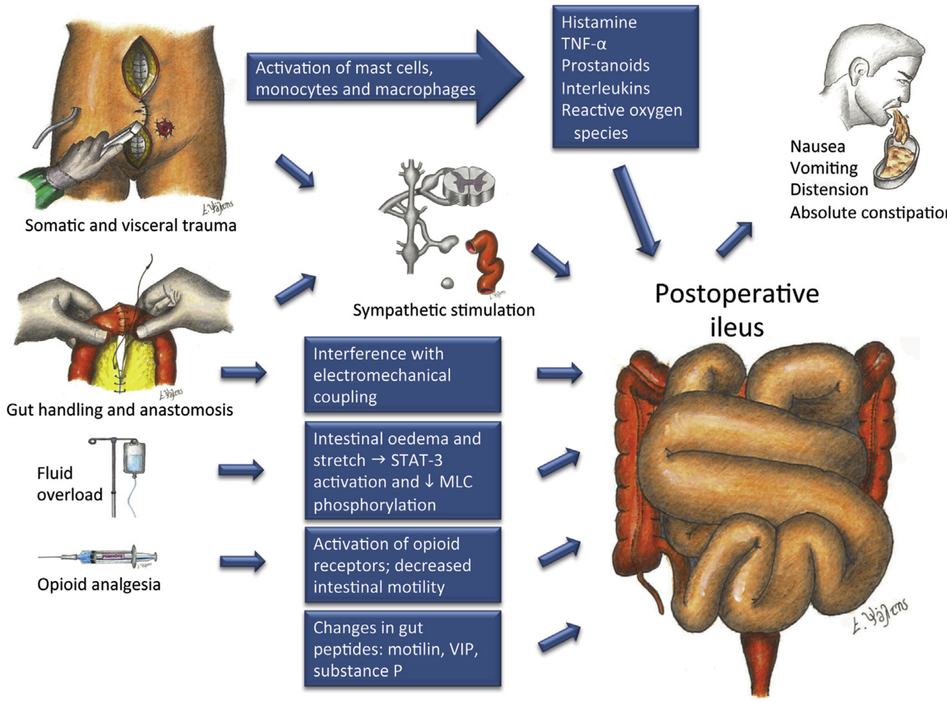

Fig. 2. Schematic diagram showing proposed mechanisms for the pathogenesis of postoperative ileus (based on data from references [28–32]). MLC = myosin light chain STAT = signal transducer and activator of transcription TNF = tumour necrosis factor VIP = vasoactive intestinal polypeptide.

Blood products are infrequently used during elective surgery, however, hyponatraemia and a large drop in haemoglobin levels are associated with prolonged ileus [24]. The mechanism is unclear, but may occur following excess crystalloid administration, leading to gastrointestinal oedema, or an increase in sympathetic and endocrine stress response inhibiting motility [15].

9. Management of POI

POI should be anticipated, and efforts to reduce its duration should begin preoperatively, and include many of the principles of enhanced recovery programmes (ERPs) aimed at limiting the stress response to surgery. Such efforts include, where possible, the use of minimal access techniques, and the use of thoracic epidural analgesia, to block sympathetic outflow and minimise opioid requirement postoperatively. Nasogastric tubes (NGTs) should not be used routinely in elective surgery [41]. NGTs should only be used selectively if there is increased likelihood of prolonged POI [42]. Examples may include after prolonged emergency surgery, gross peritoneal soiling, massive blood loss, or an open abdomen, but the evidence in emergency surgery is lacking, and is best approached on an individual case basis [43].

Initial treatment of prolonged POI consists of insertion of an NGT to relieve luminal distension, monitoring of urine output, and correction of electrolytes with intravenous fluids to achieve a balanced fluid state (Table 3). Absence of nutrition for 5–7 days should prompt a consultation with the nutritional team [44], and investigations to exclude early postoperative small bowel obstruction (SBO) and secondary causes of POI should not be delayed [25].

Table 3
Principles for management of prolonged postoperative ileus.

Restoration of normal physiology
Insertion of nasogastric tube
Accurate measurement of fluid input and output
Exclusion and treatment of secondary causes
Nutritional team consultation (≥5–7 days)

10. The evidence behind strategies for prevention of POI

Pre-, intra- and postoperative interventions can help prevent POI and the rationale for these are summarised in Table 4.

Table 4
Strategies to prevent postoperative ileus.

Intervention	Mechanism	Benefit
Salt and fluid overload	↓ gut oedema and stretch	++
Carbohydrate loading	↓ insulin resistance	±
Routine nasogastric tubes	Prophylactic drainage of stomach	−
Intravenous lidocaine	Anti-inflammatory; opioid-sparing	+
Coffee	Stimulatory effect	+
Chewing gum	Stimulatory effect	+
NSAIDs	Opioid sparing; anti-inflammatory	++
Early enteral nutrition	Anabolic; ↓ insulin resistance; stimulatory	++
ERPs	Multimodal-effect	++
Laparoscopic surgery	↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction	++
Alvimopan	μ-opioid receptor antagonist	++
Mid-thoracic epidural anaesthesia	↓ inflammatory response ↓ sympathetic stimulation ↓ opioid requirement	++
Early mobilisation	? anabolic effect	+/±
Nicotine	Colonic prokinetic	+
Daikenchuto	Anti-inflammatory on acetylcholine receptors	+
Magnesium sulphate	Anaesthetic effect	+
Prokinetics	Prokinetic effect	±

++ Definite benefit.
+ Possible benefit.
± No benefit.
- Possible harm.

10.1. Pre- and intra-operative

10.1.1. Mid-thoracic epidural analgesia (EA)

Surgery induces an increase in the catabolic hormones cortisol, glucagon and catecholamines, an effect which is attenuated by blockade of afferent pathways using EA [45]. In addition, EA is effective at promoting insulin sensitivity [46] and may decrease perioperative cytokine expression [47]. Furthermore, EA with local anaesthetic has been shown to reduce the duration of POI from its effect on inhibiting sympathetic nervous afferents to the gastrointestinal tract [32]. A Cochrane review examining the effect of EA with local anaesthetic *vs.* systemic opioids demonstrated a reduction in gastrointestinal paralysis in patients undergoing laparotomy for abdominal surgery [48] by up to 37 h (19–56 h, $P < 0.001$). Another meta-analysis [49] examining the effects of EA *vs.* parenteral opioids after colorectal surgery, demonstrated a weighted mean difference (WMD) of −1.55 days (95% CI -2.27 to −0.84 days) in duration of gastrointestinal dysfunction with EA. However, the authors did not report any appreciable differences in LOS, and adverse effects such as hypotension and urinary retention were more common in those with EA. Anastomotic leak rates were comparable in both groups. Whilst the effect EA has in laparoscopic techniques on LOS and ileus is inconclusive [50,51], the opioid-sparing benefit for this group may support its use [52].

10.1.2. Carbohydrate loading

Preoperative carbohydrate loading reduces postoperative insulin resistance [53,54] and a recent meta-analysis concluded that carbohydrate loading reduces hospital LOS by 1 day after major abdominal surgery, but not after procedures where the expected LOS is less than 3 days [55]. The effect of preoperative carbohydrate loading on reducing POI is less clear. In a small RCT [56] examining preoperative carbohydrate loading *vs.* water and *nil per os* regimens, a statistically insignificant trend was seen towards hastening gastrointestinal function. A further RCT [57] in 2014 found insignificant trends towards hastening of gastrointestinal function, but not of reducing LOS.

10.1.3. Nasogastric tubes

NGTs are used for the management of POI when vomiting and abdominal distension predominate. Routine placement of an NGT at the end of surgery in order to drain the stomach, prevent POI and ‘protect’ anastomoses is not supported by clinical studies. An updated Cochrane review examining prophylactic NGT insertion concluded that NGT usage after elective surgery did not deliver its intended benefits of hastening recovery of bowel function, decreasing pulmonary complications, improving patient comfort, protecting anastomoses or reducing hospital stay [41]. Furthermore, time to first passage of flatus occurred 0·51 days earlier [(WMD, 95% CI 0·45 to 0·56); $P < 0{\cdot}00001$] in those without an NGT. NGT usage is also associated with increased upper airway inflammation and lower airway infections [58].

10.1.4. Surgical approach

An investigation comparing gastrointestinal transit time in laparoscopic and open colorectal surgery examined time to first flatus and bowel movement, and also by following radio-opaque markers through the bowel postoperatively [59]. Three days after surgery, more of the radio-opaque markers were found in the right colon ($P < 0.01$) and fewer in the small intestine ($P < 0.05$) in laparoscopic compared with conventional patients. Five days after laparoscopic surgery, more markers had reached the left colon ($P < 0.05$) compared with conventional patients. The mean time to first passage of flatus and motion was 50 h and 70 h respectively in laparoscopic cases, and 79 h and 91 h in conventional cases ($P < 0.01$). Oral nutrition could be instituted 1.7 days earlier in laparoscopic cases. Whilst the perioperative protocols were well-standardised, this study was conducted before the broad adoption of ERPs, and all patients underwent bowel preparation, routine NGTs, graded introduction of diet and none received epidural anaesthesia.

The LAFA study [60] examined the effect of laparoscopic or open surgery, combined with fast-track or standard care, on length of hospital stay in 400 patients undergoing colectomy. Discharge criteria were well-defined, including the restoration of normal gastrointestinal function. In patients receiving fast-track care, median time to tolerate food postoperatively was 1 day in patients undergoing laparoscopic (interquartile range 1–2) and open surgery (interquartile range 1–3), whereas those receiving standard care tolerated food on the third day in those undergoing laparoscopic surgery (interquartile range 1–3) and fourth day in the open surgery group (interquartile range 2–5). Patients randomised to laparoscopic and fast-track care had a reduced LOS by a median of 1 day compared with the three other groups ($P < 0.001$). There was no significant difference in morbidity or mortality between the four groups. This study highlights the benefit of ERPs in facilitating recovery of gastrointestinal function after surgery.

10.1.5. Alvimopan

Opioids, such as morphine, are frequently used for the management of postoperative pain. ERPs advocate the use of non-steroidal anti-inflammatory drugs as part of a multimodal analgesic strategy to reduce the dosage of opioids required, but morphine is often required for breakthrough pain. μ-opioid receptors are the primary mediators of opioid analgesic effects in the central nervous system, and also the origin of gastrointestinal side effects [61].

Both endogenous opioids released directly from the gut following surgical trauma, and those administered exogenously for analgesia, adversely affect intestinal motility [18,23]. Alvimopan is a peripherally acting μ-opioid receptor antagonist, which does not cross the blood brain barrier readily.

A meta-analysis [62] examining the effect of alvimopan *vs.* placebo on POI after major abdominal surgery found that alvimopan accelerated recovery of gastrointestinal function by 1.3 days [Hazard Ratio (HR) 1.16 to 1.45 d, $P < 0.00001$] at a dose of 12 mg/day, and by 1.5 days (HR 1.14 to 1.96 d, $P = 0.003$) at a dose of 6 mg/day. Furthermore, the authors found a reduction in time for readiness for discharge of 1.4 days (HR 1.19 to 1.63 d, $P < 0.0003$) with a dose of 6 mg/day, and 1.26 (HR 1.13 to 1.40 d, $P < 0.0001$) with 12 mg/day. Postoperative analgesic effects were not diminished by the use of alvimopan, as assessed by visual analogue scales.

10.1.6. Salt and water overload

Surgery causes an increase in ADH, cortisol and aldosterone leading to salt and water retention [28]. The aim of perioperative fluid therapy is to maintain normovolaemia and end-organ perfusion. Liberal perioperative fluid administration can result in an increase of 2–3 kg of body weight, as a result of a redistribution of fluid to the interstitial space. Not only does this increase the risk of cardiopulmonary overload, but the oedema can also increase the risk of POI and anastomotic leak [28,63]. Referred to as the ‘misunderstood nephron’ [64], the gastrointestinal tract turns over up to 9 L of fluid per day. Micronutrients and electrolytes, particularly Na^+, K^+ and Cl^-, are central in both active and passive transport across the basolateral membrane and the luminal border, with an ‘enterorenal’ axis, consisting of at least 13 different hormones, responsible for the huge flux of fluid. Myosin light chains (MLCs) are central to smooth muscle contraction and intestinal transit. The Na^+/H^+ ion exchange protein (NHE) is activated by oedema-induced mechanical stretch. Phosphorylation of MLC is inhibited by NHE which reduces contractility, providing a clue to the mechanism behind the inhibition of peristalsis resulting from oedema-induced mechanical stretch [28] (Fig. 2).

Both under and over administration of fluid lead to complications, and a balanced fluid state utilising goal-directed therapy techniques, such as oesophageal Doppler, LiDCO (LiDCO Ltd, Cambridge, UK) or PiCCO (Philips Healthcare, The Netherlands) should be utilised to achieve this [28].

10.1.7. Intravenous lidocaine

The use of intravenous lidocaine perioperatively has been reported to confer analgesic benefits, increase the rate of gastrointestinal recovery, and dampen plasma levels of the cytokines interleukin IL-1, IL-6 and IL-8 [65]. These benefits have not been demonstrated in extra-abdominal surgery [65]. Various regimens are followed, but lidocaine is typically administered as an IV bolus (1.5–2 mg/kg) followed by a continuous infusion at 1.5–3 mg/kg/h for up to 24 h postoperatively. A meta-analysis of lidocaine *vs.* controls was conducted investigating postoperative analgesia and recovery in patients undergoing abdominal surgery [66]. This demonstrated improved pain scores at 6 and 24 h postoperatively in patients receiving intravenous lidocaine *vs.* controls [66]. Total opioid consumption was reduced in those receiving lidocaine *vs.* controls. Mean time to first passage of flatus was shortened when compared with controls, with a WMD of −6.92 h (95% CI: -9.21 to −4.63; $I^2 = 62.8\%$), and time to first bowel movement was significantly shorter in the lidocaine group, with a WMD of −11.74 h (95% CI: -16.97 to −6.51; $I^2 = 0$). There was no significant difference in LOS when patients in the lidocaine group were compared with controls. Side effects were mild and none required therapeutic intervention.

10.1.8. Intravenous lidocaine vs. thoracic epidural analgesia

A randomised clinical trial comparing TEA with intravenous lidocaine demonstrated similar postoperative pain scores, duration of ileus, and LOS after colorectal surgery [67]. A similar study also examined levels of pro-inflammatory markers, and concluded that although TEA demonstrated the best clinical outcomes, intravenous lidocaine had better pain scores, gastrointestinal recovery and anti-inflammatory response compared with controls [68]. A randomised clinical trial conducted in the context of an ERP demonstrated similar resumption of gastrointestinal function between intravenous lidocaine and TEA, but better analgesia with TEA in patients undergoing rectal surgery [69].

10.2. Postoperative

10.2.1. Coffee

The effect of coffee on postoperative ileus was examined in an open-label trial on 80 patients undergoing open or laparoscopic colectomy, randomised to receive 3 cups of 200 ml coffee or water per day [70]. Those receiving coffee passed stools at 60.4 h, and those in the water group at 74 h ($P = 0.006$). However, variable quantities of laxatives were prescribed, patients had a mean LOS of over 11 days (questioning the adherence to ERPs), and the anastomotic leak rate tended to be higher in the control arm (12.8% *vs.* 2.5%, $P = 0.083$).

10.2.2. Prokinetics

A multimodal approach is recommended to prevent and treat postoperative nausea and vomiting [71]. Combination of 5-HT_3 receptor antagonists with dexamethasone has been shown to be particularly effective [72]. Investigations as to whether prokinetics can be used to ameliorate POI have been unsuccessful. A Cochrane review from 2008 identified four trials investigating metoclopramide, and four trials investigating erythromycin, found no significant effects on time to flatus, bowel movements or tolerance of oral intake, however the quality of the studies reported was moderate to poor [73].

Mosapride is a gastroprokinetic agent that acts as a selective 5-HT_4 agonist. Two clinical trials following colonic resection have investigated its use as a prokinetic agent. An RCT of mosapride usage after hand-assisted laparoscopic colectomy for cancer [74] showed a reduction of time to first flatus of 32.7 *vs.* 39.1 h in controls, first bowel movement occurring at 48.5 *vs.* 69.3 h, and a reduction in gastric emptying and length of hospital stay (6.7 *vs.* 8.4 days). In a subsequent RCT of laparoscopic colectomy for cancer [75], patients receiving mosapride on average passed flatus at 52.2 *vs.* 98.1 h in controls, stools at 84.7 *vs.* 122.7 h and had a higher total food intake in the immediate postoperative period. It has been suggested that the effect of mosapride on reducing POI may be due to the anti-inflammatory action it has on the gastrointestinal tract [76].

10.2.3. NSAIDs

NSAIDs inhibit cyclooxygenase (COX) pathways, and their use is advocated as part of a multimodal postoperative analgesic strategy in reducing opioid consumption. There is evidence from animal studies [77] and human clinical trials [78] that COX-2 inhibition may shorten POI. An RCT was conducted consisting of 210 patients undergoing major abdominal surgery. Patients received twice daily celecoxib (100 mg, $n = 74$), diclofenac (50 mg, $n = 69$) or placebo ($n = 67$). A reduction in POI rates was demonstrated in those receiving celecoxib (1 patient *vs.* 7 in the diclofenac and 9 in the placebo arms) [78]. Interestingly, there were no differences in opioid consumption between arms.

NSAID usage can inhibit leukocyte accumulation at sites of inflammation and may impair healing, particularly at anastomoses. This important question has arisen within the scientific community, and several published studies have shown conflicting results [79–84].

10.2.4. Chewing gum

Chewing gum is thought to simulate sham feeding that may stimulate gastrointestinal recovery postoperatively. A meta-analysis of 17 studies examining chewing gum after abdominal surgery was reported by Li et al. [85]. The authors demonstrated favourable results for gum chewing in time to first flatus of −0.31 d WMD (95% CI, -0.41 to −0.19; $P < 0.0001$), time to first bowel movement of −0.51 d WMD (95% CI, -0.73 to −0.29; $P < 0.0001$) and LOS of −0.72 d WMD (95%CI, -1.02 to −0.43; $P < 0.0001$). Subgroup analysis on those undergoing laparoscopic surgery, which can accelerate recovery, did not demonstrate any benefit of gum chewing.

10.2.5. Early oral nutrition - elective

The most recent meta-analysis of early oral nutrition [86] advocates its use for reduction in POI, examining markers of ileus (time to flatus, vomiting and NGT reinsertion). There is clear evidence that early oral nutrition has a beneficial effect on reducing LOS [87], infectious complications [88], nitrogen waste and gut hyperpermeability [89], without increasing the risk of anastomotic leakage [87,90]. Early enteral nutrition has become a core principle in multimodal ERPs. The effect of this individual component on preventing or reducing POI has generally been examined outwith ERPs, and protocols for introduction of diet vary considerably even within intervention arms [91]. A study examining the effect of nutrition on POI randomised patients undergoing major rectal surgery to either early enteral nutrition ($n = 61$) or early parenteral nutrition (n = 62) [92]. The time taken to first passage of stool was significantly shorter in those receiving early enteral nutrition compared with early parenteral nutrition. Furthermore, there was a significant increase in the anastomotic leak rate in those receiving parenteral nutrition (9 *vs.* 1) [92]. Vomiting has also been seen to occur more frequently among those receiving early oral nutrition, but rates of nasogastric tube insertion are not increased [93]. Time to first flatus and defecation is typically reduced in patients receiving early oral nutrition. Although the exact effect early oral nutrition has as part of multi-modal ERPs is difficult to quantify [94], efforts have been made to investigate early oral nutrition outside of ERAS programs, and have demonstrated similar hastened gut function [95]. A Cochrane review in 2011 examining early oral nutrition and postoperative complications did not specifically examine the concept of POI [96], but found no benefit in delaying feeding. Some of the principles of ERPs may overlap with emergency surgery, and further work in this field is required [97].

10.2.6. Laxatives

Studies primarily examining the effect of laxatives have mainly been conducted in gynaecological surgery [98,99], although their use is documented in colorectal surgery as part of a multi-modal rehabilitation programme [100]. A randomised controlled trial was conducted in women undergoing abdominal hysterectomy [101]. Fifty-three women were randomised to receive postoperative laxatives (oral magnesium oxide) or placebo. The median time to first postoperative defecation was 45 h *vs.* 69 h in the placebo group ($P < 0.0001$). Vomiting, nausea and pain scores showed no differences between the groups. A study investigated the effect of postoperative laxatives and oral nutritional supplements on gastrointestinal function in 68 patients undergoing liver resection, in the context of an ERP. Patients were randomised to receive either, or both, of laxatives and oral nutritional supplements in a 2×2 design. Those receiving laxatives passed stool at 4 days (3–5 d), those not receiving laxatives, at 5 days (4–6 d); $P = 0.034$. Oral nutritional supplementation did not affect gastrointestinal recovery. Other secondary outcomes including the time to first consumption of fluid and food, overall time to functional recovery, and gastric emptying time (stable isotope breath test) were also investigated, but none were affected by oral nutritional supplementation or laxatives.

11. Potential future therapies

A number of interventions to reduce the duration, or treat prolonged POI are currently being investigated. The safety of these are yet to be determined and widespread use is not advocated.

11.1. Water soluble contrast agents

Gastrografin is a water-soluble contrast medium that is used for gastrointestinal diagnostic purposes. Owing to its high osmolarity, its actions are similar to those of osmotic laxatives, which cause the retention of a large amount of fluid in the gastrointestinal tract. This is useful for the treatment of conditions such as meconium ileus [102]. Differentiating a functional from a mechanical small bowel obstruction is important, and gastrografin is often used for this. A recent systematic review and meta-analysis found that if contrast reached the colon within 4–24 h of administration, obstruction was likely to resolve without an operation in 99% of patients [103]. If contrast did not reach the colon, obstruction was unlikely to resolve without operation in 90% of patients. Patients investigated in this way had a mean-weighted difference in LOS of −1.87 days (95% CI -2.21 to −1.52, $P < 0.001$), emphasising its benefit as both a diagnostic and therapeutic agent. The role for its use in POI is less clear, and the results of a randomised controlled trial from New Zealand are awaited.

11.2. Nicotine

Nicotine receptors are found in pre- and paravertebral ganglia, colonic intrinsic and extrinsic nerves. Administration of nicotine induces acceleration in colonic transit followed by relaxation of the descending colon [104], an effect that may be due to rapid tachyphylaxis. A reduction in total colonic transit time following nicotine administration has also been demonstrated in healthy volunteers [105]. Nicotine also suppresses TNF, macrophage inflammatory protein 2, and IL-6 release from peritoneal macrophages [106].

11.3. Daikenchuto

Daikenchuto, a traditional Japanese herbal medicine comprised of three different herbs (dried ginger root, ginseng, and zanthoxylum fruit) is prescribed for patients with abdominal distension in Japan [107]. The benefits of this medicine have been studied in rodents [108], pointing to a reduction in POI by its anti-inflammatory action on nicotinic acetylcholine receptors [109]. Results from small clinical trials examining a hastening of gut function following gastrectomy [110] and colorectal surgery [111,112] are encouraging, and a further trial after pancreaticoduodenectomy is ongoing [113].

11.4. Magnesium sulphate

Magnesium has a complex relationship with calcium channels and the nervous system, and is used to prevent seizures during pre-eclampsia, to block adrenergic response in pheochromocytoma surgery, and for cardiac dysrhythmias. It is also an N-methyl-D-aspartate receptor antagonist thought to be involved in the perception of pain [114]. Several meta-analyses have demonstrated a reduction in postoperative opioid usage following intraoperative administration of magnesium [115,116]. A small RCT [114] specifically examining the use of magnesium and its effect on ileus found a decrease in POI of 1.9 days *vs.* control. However, the diagnosis of POI was made from a retrospective record of the commencement of oral intake from the medical notes.

12. Conclusions

POI is often an inevitable event after surgery, and is associated with significant morbidity, mortality and cost burden. Advances in perioperative care, particularly with the utilisation of evidence-based ERPs, appear to significantly reduce the duration of POI.

The move towards reducing the initial obligatory POI has been successful, but may have distracted from a need to manage those who develop a prolonged POI, where there is almost no evidence-based therapy. Further work into the active treatment of prolonged POI, needs to be undertaken.

Knowledge of the pathophysiology of POI continues to increase, and as more novel interventions begin to emerge, there is a clear requirement for researchers to harmonise their approach. Through standardisation of perioperative care, and the use of classification systems in the diagnosis of POI, realistic benefits may be drawn from future research in order to better-serve our patients.

Conflict of interest

DB, AME-S, EP and CAM-A have no conflicts of interest to declare. DNL has received research funding, speaker's honoraria

and travel expenses from Fresenius Kabi, BBraun and Baxter Healthcare Corporation for unrelated work and has served on Advisory Boards for Baxter Healthcare Corporation and AbbVie.

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Data interpretation: DB, AME-S, EP, CAM-A, DNL.
Writing of manuscript: DB, AME-S, DNL.
Drawing of figures: EP, DB, DNL.
Critical revision: DB, AME-S, EP, CAM-A, DNL.
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