Postoperative ileus: Pathophysiology & treatment strategies
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Chapter 1

New therapeutic strategies for postoperative ileus

Adapted from:

New therapeutic strategies for postoperative ileus.
Abstract

Patients undergoing an abdominal surgical procedure develop a transient episode of impaired gastrointestinal motility or postoperative ileus. Importantly, postoperative ileus is a major determinant of recovery after intestinal surgery and leads to increased morbidity and prolonged hospitalization, which is a great economic burden to health-care systems. Although a variety of strategies have been shown to reduce postoperative ileus, including multimodal postoperative rehabilitation (fast-track care) and minimally invasive surgery, none of these has been completely successful in shortening postoperative ileus. The etiology of postoperative ileus is multifactorial, but recent advances into the insight of the pathogenesis of postoperative ileus have identified intestinal inflammation triggered by surgical handling as the main mechanism. The importance of this inflammatory response in postoperative ileus is underscored by the beneficial effect of pharmacological interventions blocking the influx of leukocytes. New insights into the pathophysiology of postoperative ileus as the involvement of the innate- and the adaptive (T-helper type 1 cell-mediated immune response) immune system offer interesting and important new approaches to prevent postoperative ileus. In this review, we discuss the latest insights into the mechanisms behind postoperative ileus and new strategies to intervene in the postoperative inflammatory cascade.
**Introduction**

Postoperative ileus is an iatrogenic condition characterized by a transient cessation of coordinated propulsive motility. Postoperative ileus can occur after intestinal surgery and leads to increased morbidity and prolonged hospitalization. Postoperative ileus also generates a significant burden to healthcare cost. Two large prospective cohort studies in the USA and the UK have demonstrated that gastrointestinal dysfunction is the most common type of postoperative complication after major non-cardiac surgery.\(^1\), \(^2\) In a retrospective cohort study of patient records from >500 hospitals in the USA, ileus was found to be an important predictor of extended postoperative hospital stays and costs in patients undergoing colectomy.\(^3\) The economic burden of postoperative ileus has been estimated to exceed US $750 million per year and, interestingly, postoperative ileus was as expensive as managing severe postoperative complications (e.g. deep venous thrombosis, pulmonary embolism, surgical site infection) that might not lead to ileus.\(^4\) The possible benefits of improved and effective management of postoperative ileus include reduced use of resources, fewer complications and shortened hospital stay. In this Review, we discuss the latest insights in the mechanisms and treatment of postoperative ileus and focus on new therapeutic approaches that involve intervention in the inflammatory cascade.

**Mechanisms of postoperative ileus**

Postoperative ileus is immune-mediated

Since the beginning of the 20th century, postoperative ileus has been recognized as a highly prevalent consequence of abdominal surgery and the inhibition of gastrointestinal motility induced immediately after surgery was shown to primarily result from anaesthetics and opioid analgesics. Moreover, handling of the intestine during surgery activates inhibitory neuronal reflexes\(^5\), \(^6\), \(^7\) involving adrenergic and non-adrenergic pathways\(^8\), \(^9\) and leads to intestinal oedema by excessive intravascular fluid loading.\(^10\) These events, however, fail to explain the prolonged inhibition of gastrointestinal motility seen during several days after abdominal surgery. At the end of the 20th century, the inflammatory-mediated ileus hypothesis was introduced, derived from data illustrating that inflammation of the intestinal muscularis externa is the main mechanism underlying postoperative ileus.\(^11\) Handling of the intestine during abdominal surgery activates resident innate immune cells located within the muscularis externa, triggering the release of inflammatory cytokines and chemokines, as well as increased expression of adhesion molecules on endothelial cells, which causes circulating leukocytes (mainly neutrophils and monocytes) to invade the muscularis externa.\(^11\) Invading monocytes
and activated resident macrophages produce nitric oxide and prostaglandins, compromising the contractile activity.\textsuperscript{12} This inflammatory response has also been confirmed in human intestinal surgical samples,\textsuperscript{13, 14} and is now considered to mediate impaired contraction of handled and inflamed tissue.\textsuperscript{15} Postoperative ileus, however, is not restricted to the small intestine but involves the entire gastrointestinal tract.\textsuperscript{16} The mechanisms underlying the generalized inhibition of gastrointestinal motility in response to this local inflammation comprise a complex neuronal and immunological response involving leukocytic production of nitric oxide,\textsuperscript{12} panintestinal dissemination of inflammation mediated by T helper (T\textsubscript{H}) cells, and activation of inhibitory neural pathways that affect the entire gut.\textsuperscript{17}

**Innate and adaptive inflammatory mediators**

Although the influx of neutrophils and monocytes into the muscularis externa of the small bowel has been shown to underlie impaired gut motility after intestinal manipulation, the initial trigger of the inflammatory cascade is unclear and could involve dendritic cells, mast cells and/or macrophages.\textsuperscript{12, 18} In mouse studies, peritoneal mast cells were activated, which caused a subsequent release of mast cell mediators and an inflammatory response in the intestine.\textsuperscript{17} In humans, intestinal manipulation during abdominal hysterectomy caused an immediate release of mast-cell activation marker tryptase in the peritoneal fluid followed by an increase of pro-inflammatory cytokines IL-6 and IL-8. Patients who underwent minimally invasive surgery had lower levels of mast cell activation compared with those who had intestinal contact during open surgery\textsuperscript{14} indicating that the degree of intestinal handling correlated with the level of mast cell activation and the subsequent inflammatory response. Moreover, mast-cell deficient Kit\textsuperscript{W}/Kit\textsuperscript{WV} mice failed to develop inflammation in the intestinal muscularis externa after surgery and reconstitution of mast cells in those mice restored the handling-induced inflammation in the intestine.\textsuperscript{18}

An important feature of postoperative ileus is that it has a disseminated nature, whereby motility of the entire gastrointestinal tract is impaired even if only part of the intestine has been handled or is inflamed. Activation of inhibitory neural pathways by inflammatory mediators, such as cytokines and prostaglandins, has been proposed as the underlying mechanism.\textsuperscript{17, 19} An alternative theory is that the inflammatory response is disseminated by memory T cells to unmanipulated areas of the gastrointestinal tract, which could underlie the panenteric nature of postoperative ileus.\textsuperscript{12} Intestinal manipulation could stimulate resident dendritic cells to release IL-12 and trigger T\textsubscript{H}1 memory cells to egress into the systemic circulation and migrate to non-manipulated areas of the intestine. These T\textsubscript{H}1 memory cells release IFN-\gamma, which results in stimulation of macrophages in the muscularis externa and dissemination of the inflammatory response.\textsuperscript{44}
The vagal anti-inflammatory pathway

During the past decade, the importance of the vagus nerve in regulation of intestinal immunity was established. In a rat model of sepsis, electrical stimulation of the vagus nerve was shown to reduce tumour necrosis factor (TNF) levels, indicating that inflammation had been decreased, and to improve survival. Neuronal acetylcholine receptor α7 signalling is involved with mediating the effects of vagus nerve stimulation. The anti-inflammatory effect of the vagus nerve is part of a reflex by which the brain senses inflammatory information in the periphery through vagal afferents and subsequently creates an integrated anti-inflammatory response through vagal efferent fibres. Our research group showed in a mouse model of postoperative ileus that electrical stimulation of the vagus nerve reduces macrophage activation, dampens intestinal muscular inflammation and improves postoperative ileus. Moreover, immune cells in the intestinal wall are in close proximity to cholinergic nerve fibres further demonstrating that interaction between the nervous system and immune system is an important mechanism that modulates intestinal inflammation. The cholinergic neuronal circuitry can also be centrally stimulated pharmacologically by intracerebroventricular injection of semapimod (tetravalent guanyl-hydrazone known as CNI-1493) or muscarinic agonist receptor (McN-A-343) or by intravenous injection of a ghrelin agonist or acetylcholinesterase inhibitor (galantamine). Moreover, the ‘cholinergic inflammatory reflex’ is also activated through enteral feeding of lipid-rich nutrition. These different interventions reduce manipulation-induced inflammation of the intestine and accelerate recovery of gastrointestinal motility in rodent models of postoperative ileus. Interestingly, jatrohhizine, an alkaloid isolated from medicinal plants, dose-dependently increased gastrointestinal transit in a rat model of ileus by activation of the cholinergic pathway.

Our research group used a retrograde neuronal tracer, which travels along neurons and can be used to show neural connections from the periphery to the central nervous system, to show that intestinal inflammation triggers a vagus-nerve-mediated circuit leading to activation of vagal motor neurons in the brainstem that are connected to the inflamed intestine. These findings demonstrate that the anti-inflammatory pathway is indeed a hard-wired neural circuit.

From bench to bedside

Considerable progress has been made in understanding the mechanism behind postoperative ileus using experimental animals and several translational studies show that the pathophysiological mechanisms described above could be applicable to humans. However, it should be emphasized that data obtained in animal models might not necessarily translate to humans. For example, there are differences in mediators and receptor expression profiles between humans and
rodents; the presence of comorbidity, such as diabetes and hypertension is difficult to model in experimental animal studies; and the type of surgery studied. Moreover, there is a need for reliable outcome measures to evaluate clinical success in new drug trials. Parameters such as first defecation and flatus are often used as primary outcome parameters in clinical trials; however, these parameters are rather unreliable. Time to first flatus strongly depends on patient reporting, and passage of stool might simply reflect rectal emptying and provide no reliable information on recovery of whole gut transit. Thus, with novel treatments for postoperative ileus in development, there will be a definite need for more reliable outcome parameters in order to evaluate new treatments.

Current postoperative ileus therapies
Multimodal enhanced recovery programs

As postoperative ileus is a multifactorial disorder, a multimodal approach to shorten the duration of disease has been advocated. Enhanced recovery after surgery (ERAS) protocols or fast-track programmes have been introduced in several surgical centres in order to accelerate recovery of gastrointestinal function, improve clinical outcome and reduce hospital length of stay. In these programmes, several perioperative measures including improved perioperative fluid management, early ambulation and feeding and optimal analgesia are incorporated into patient management to reduce the rate of perioperative morbidity.

Laparoscopic surgery

Minimal invasive surgery using laparoscopy has many potential advantages over conventional open surgery, including smaller incisions, reduced pain and inflammation, earlier gastrointestinal recovery and shorter hospital stay. Several studies and a 2012 meta-analysis that included 4614 patients with colon cancer demonstrate that laparoscopic surgery significantly reduces time until recovery of bowel function (by 1 day on average) and duration of hospital stay compared with open colonic resections. Furthermore, postoperative ileus occurs more frequently after conventional laparotomy than mini laparotomy for the resection of colorectal cancer. Therefore, minimally invasive surgery and fast-track perioperative care are likely to decrease the risk and/or duration of postoperative ileus.

Prokinetics, local anaesthetics and laxatives

A Cochrane review that evaluated the benefits of prokinetic agents including cisapride, erythromycin, cholecystokinin and dopamine antagonists indicated that routine administration of prokinetics for prevention of postoperative ileus is not recommended. The effectiveness of these agents is probably reduced as
contraction of the inflamed gastrointestinal smooth muscle is strongly compromised by the inflammatory process. Metoclopramide is a dopamine D2 receptor antagonist with mixed 5-HT₃ receptor antagonistic and 5-HT₄ receptor agonistic properties. It is commonly used to treat nausea and vomiting and to promote gastric emptying, especially in patients with diabetes mellitus and gastroparesis.⁴⁹ These prokinetic characteristics of metoclopramide have led to evaluations of the drug as potential treatment of postoperative ileus. Clinical studies have reported conflicting results, with some demonstrating a reduction in time until first bowel movement and resumption of oral soft diet⁵⁰ and some showing no effect.⁵¹ Moreover, the number of patients included in these trials was low (only 16 per group), which makes it difficult to draw any solid conclusions and, therefore, further studies are required.

Epidural local anaesthetics, for postoperative analgesia, used in conjunction with fast-track care minimize systemic opioid use and shorten the duration of postoperative ileus.⁴ Hence, epidural analgesia is included in most published ERAS protocols, and has been advocated in a recent published consensus review.₃⁷ Laxatives such as bisacodyl or magnesium oxide are commonly used as part of a multimodal approach to manage postoperative ileus³ and preliminary studies have been positive. Laxatives are inexpensive treatments but further studies are required before general recommendations are made.³⁴

Alvimopan

Opioid agonists are often used for postoperative analgesia and, in combination with endogenously released opioids, contribute to postoperative ileus by decreasing intestinal motility through stimulation of μ-type opioid receptors in the gut.⁵² Alvimopan is a peripherally-acting μ-opioid-receptor-antagonist. It belongs to a new class of drugs designed to reverse opioid-induced gastrointestinal effects without affecting the centrally-mediated analgesic effects of opioids and, therefore, not compromise pain relief.⁵³ A pooled, post-hoc analysis of four randomized, double-blind, placebo-controlled, phase III trials⁵⁴-⁵⁷ showed that alvimopan led to a reduction in the time until tolerance of solid food and bowel movement and a statistically significant reduction in the duration of hospital stay⁵⁸. Hence, FDA approval was granted in 2008. However, the use of alvimopan was recently associated with an increased rate of myocardial infarction, limiting its clinical application.⁴⁸, ⁵³ Only one phase III trial was conducted outside North America and assessed the effect of alvimopan on postoperative bowel recovery after open abdominal surgery carried out at 70 hospitals in 11 countries, predominantly within the European Union.⁵⁹ The study showed a potential benefit although it was not statistically significant, possibly as the opioid doses used in this trial were low.⁴⁵, ⁵⁹ The drug was cost saving, although this has not yet been thoroughly assessed for treating patients undergoing laparoscopic surgery, but randomized, double-blind,
controlled trials are currently running in the USA,\textsuperscript{60} to determine its therapeutic and cost saving potential in patients undergoing laparoscopic colonic resection.\textsuperscript{61}

**Therapies currently in clinical trials**

Improved knowledge of the pathophysiology of postoperative ileus has led to development of new compounds to use as new therapies. A number of drugs and approaches are currently in clinical development.

**Methylnaltrexone**

Methylnaltrexone is a peripherally acting $\mu$-type opioid receptor antagonist that does not readily cross the blood-brain barrier. Similarly to alvimopan, methylnaltrexone has been evaluated as potential treatment for postoperative ileus. In a phase II study, 65 patients who underwent segmental colectomy received 0.3 mg/kg methylnaltrexone or placebo intravenously every 6 hours starting at 90 minutes after surgery and continuing either for up to 24 hours after gastrointestinal recovery or for up to 7 days. Compared with placebo, methylnaltrexone led to a statistically significant reduction in the time until tolerance of solid food and bowel movement and significantly reduction in time to hospital discharge by one day.\textsuperscript{62, 63} However, two recent, placebo-controlled phase III trials evaluating the use of intravenous methylnaltrexone at doses of 12 mg and 24 mg in 1048 patients undergoing segmental colectomy failed to show improvement of postoperative ileus and time to hospital discharge (Table 1).\textsuperscript{64}

**Lidocaine**

Local anesthetics such as lidocaine reduce pain perception and also decrease inflammation.\textsuperscript{65} Lidocaine can promote gut motility by blocking the afferent and/or efferent arms of the sympathetic inhibitory spinal and prevertebral reflexes, which are involved in ileus. Moreover, lidocaine decreases sympathetic nervous system activity\textsuperscript{66} and has a direct excitatory effect on intestinal smooth muscle.\textsuperscript{67} In six clinical studies (including 116 patients) intravenous administration of lidocaine (1–3 mg/min) during 4 or 24 hours after surgery shortened the time until the return of bowel function (1 day earlier than saline) and shortened the length of hospital stay.\textsuperscript{65, 68-72} It should be emphasized though those results varied with the type of resection and surgical approach and that the exact mechanism of action remains unclear.
Ghrelin agonists

Ghrelin is an orexigenic hormone mainly produced in the fundus of the stomach and in the pancreas. Recent rat studies using ghrelin as treatment of sepsis provide evidence for the anti-inflammatory properties of ghrelin. Administration of ghrelin or a ghrelin agonist before surgery seems therefore a promising therapeutic strategy to prevent the onset of intestinal inflammation and thus ileus. Agonists of ghrelin such as TZP-101 (ulimorelin hydrochloride have powerful prokinetic properties, and are being evaluated as potential therapies for postoperative ileus. However, ghrelin activates an anti-inflammatory pathway and improves inflammatory conditions such as colitis, ischaemia reperfusion injury and sepsis. It is not clear if the anti-inflammatory properties contribute to the beneficial effect of ghrelin agonists on postoperative ileus. Nevertheless, TZP-101 effectively prevented ileus in a rat model of postoperative ileus. Perioperative intravenous treatment with 0.03–1 mg/kg with TZP-101 at 0, 2 and 4 hours after surgery improved gut transit and increased faecal pellet output. Two phase IIb studies have assessed TZP-101 safety and efficacy in postoperative ileus management. Treatment with 20–600 µg/kg TZP-101 by 30-minute intravenous infusion within 1 hour of surgical closure, then daily for up to 7 days, decreased the time to first bowel movement and shortened hospital stay. In the other phase IIb study, the effect of TZP-101 treatment (480 µg/kg) was tested in 168 patients who...
underwent colonic surgery and showed similar results. TZP-101 is currently being evaluated in a phase III clinical trial as a result of these promising findings.

5-HT4 receptor agonists

5-hydroxytryptamine receptor 4 (5-HT4) agonists such as cisapride, mosapride and prucalopride are potent prokinetic agents that exert effects in the upper and lower gastrointestinal tract. Although several studies have demonstrated improvement of postoperative ileus with cisapride, this compound has been withdrawn from the market because it caused cardiovascular adverse events in some patients. However, treatment with 15 mg of mosapride citrate taken orally three times a day (starting on day 1 after surgery) reduced postoperative ileus in 15 patients who underwent colectomy. Interestingly, a recent preclinical study showed that mosapride and another 5-HT4 agonist (CJ-033,466) improved postoperative ileus in rats by reducing the inflammatory response evoked by surgery. The improvement if postoperative ileus was mediated by activation of cholinergic myenteric neurons and resulted in suppression of resident muscular macrophages, but it is unclear whether the immunosuppressive effects would also occur in humans. Prucalopride is a selective, high-affinity 5-HT4 agonist, which is used as a treatment for chronic idiopathic constipation. Prucalopride in combination with granisetron (a 5-HT3 receptor antagonist) improved gastrointestinal transit in a rat model of postoperative ileus. In humans, prucalopride was safe and well tolerated in a phase II trial for postoperative ileus. In a study that included 317 patients who underwent partial colectomy, 0.5 mg, 2 mg or 4 mg prucalopride once daily until the third day after surgery led to faster recovery of gastrointestinal motility, and a 10% increase in the number of patients released from hospital in <6 days in the group taking 4 mg of prucalopride compared with the placebo group. Phase III studies evaluating this compound as treatment for postoperative ileus are planned.

COX-2 inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen are inhibitors of cyclooxygenase 2 (COX-2), which is also known as prostaglandin G/H-2 synthase, and prevents arachidonic acid conversion to prostaglandin H2. Interestingly, postoperative ibuprofen use was associated with decreased risk of postoperative ileus in women undergoing primary staging and debulking for ovarian carcinoma. Novel COX-2 inhibitors have been developed to achieve the analgesic, antipyretic, and anti-inflammatory activity effects of the non-selective COX inhibitor ibuprofen and other NSAIDS without gastrointestinal ulceration. These COX-2 inhibitors are commonly used in postoperative care for their analgesic properties and as part of multimodal early recovery protocols. As prostaglandins have been
proposed to have a crucial role in reducing gastrointestinal motility following surgery, selective COX-2 inhibitors administered prior to surgery should, theoretically, improve postoperative ileus. In animal models, COX-2 inhibition did indeed reduce the delay in gastrointestinal transit and diminished intestinal inflammation. A clinical trial in which patients were given 100 mg of oral celecoxib failed to confirm these findings because it did not accelerate recovery of bowel motility, although the incidence of severe or very prolonged paralytic ileus was reduced from 13.4% in the placebo group to 1.3% in the active treatment group. More promising results were obtained with 40 mg oral valdecoxib in a study involving 80 patients undergoing elective colorectal resections. Valdecoxib was administered as close as possible to the start of surgery and each subsequent dose was given at 24 hour intervals up to a maximum of 120 hours. This treatment regimen resulted in a reduction of time to first bowel sound and movement, first passage of flatus and tolerance of solid diet together with a reduction in the discharge from hospital by two days.

Gum chewing

Four studies and a meta-analysis of nine prospective randomized trials investigated gum chewing as treatment for postoperative ileus. Daily gum chewing was started after colorectal surgery and led to a decrease of 1 day in the duration of postoperative ileus, with no adverse effects. However, no benefit was seen after laparoscopic gastrointestinal surgery and length of hospital stay was not significantly reduced. The exact mechanism of action remains unclear, but it is possible that sham stimulation of the vagus nerve could trigger the cholinergic anti-inflammatory pathway. Although chewing gum would be safe, simple and cheap strategy the therapeutic effect seems rather limited.

Future therapeutic strategies

Mast cell stabilizers

The mast cell stabilizers ketotifen and doxantrazole reduced muscular inflammation and shortened disease in a mouse model of postoperative ileus, which led to a pilot study in which 60 patients undergoing abdominal surgery were treated with 4 or 12 mg ketotifen for 6 days. Although gastric emptying was statistically significant improved by ketotifen, no improvement of colonic transit was observed. More potent mast cell stabilizers might be more effective. An alternative approach might be to block intracellular tyrosine-protein kinase Syk, one of the critical tyrosine kinases involved in mast cell degranulation. Perioperative oral administration of a Syk inhibitor (1 mg/kg) statistically significant improved recovery in mouse model of postoperative ileus.
Chapter 1 | Therapeutic Strategies

### Blocking adhesion molecules and integrins

One of the first events leading to extravasation of leukocytes into the manipulated intestine is the upregulation of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), which can be induced by a number of proinflammatory cytokines such as IL-1β, TNF, IFN-γ, and is expressed by vascular endothelial cells and subsets of leukocytes. In rats, increased ICAM-1 expression is found in the microvasculature and endothelial network in the intestinal muscularis 3 hours after abdominal surgery and raised levels are sustained up to 24 hours. Treatment before and after surgery (at 3, 6 and 12 hours) with a mixture of monoclonal antibodies against ICAM-1(1A29), β2-integrins (CD11a/CD18 and CD11b/CD8), which are expressed by leukocytes, prevents immune cell infiltration within the muscularis externa. Even more a single injection prior to surgery with a mixture of the two adhesion blocking molecules anti-ICAM 1 (anti-CD54) and anti-LFA-1 (CD11a) antibodies prevented leukocyte infiltration and ameliorated gastroparesis. The ICAM-1 antisense oligonucleotide ISIS 3082 also prevented manipulation-induced inflammation and delayed gastric emptying. Taken together, these data suggest that targeting adhesion molecules could be an useful approach to prevent postoperative ileus in humans.

### Other potential new therapeutic strategies

Glycine has immunomodulatory effects in transplantation and sepsis, inhibiting the inflammatory reaction of macrophages and neutrophils by binding to specific glycine-gated chloride channels, subsequently modulating intracellular calcium concentrations. Glycine-gated chloride channels are localized to muscularis externa macrophages and infiltrating leukocytes. Moreover, in a rodent model of postoperative ileus, preoperative glycine treatment statistically significantly attenuated the inflammatory response and improved postoperative gastrointestinal transit. Thus, therapeutic modulation of resident macrophages by glycine could be a novel pharmacological strategy.

Matrix metalloproteinase (MMP)-9, a member of the gelatinase family of MMPs, is upregulated following intestinal manipulation that leads to leukocyte migration into the intestinal muscularis externa. Inhibition of MMP-9 reduces the number of infiltrating inflammatory cells and prevents the surgically-induced reduction in contraction of bowel smooth muscle mice. Depleting DCs, the use of immunosuppressants such as anti-IL-12 antibodies or inhibiting Th1 cell migration by FTY-720 could reduce postoperative ileus, although these approaches should be used with caution because of the risk of increasing the risk of infection.
Conclusions

Postoperative ileus is a major contributor to increased length of hospital stay and health care costs for patients undergoing intestinal surgery. Its pathophysiology is multifactorial but activation of a local inflammatory response within the intestinal muscularis externa has become an accepted pathophysiological mechanism, opening a new avenue of potential targets for treatment. Inhibiting intestinal macrophage or mast cell function, or intervening in the adaptive immune response and systemic spread of inflammation might reduce the duration of postoperative ileus in patients following abdominal surgery. In addition, improvements in recovery time have been obtained since the introduction of laparoscopic surgery, and with perioperative strategies such as fast-track care.

Review criteria

PubMed was searched in March 2012 for full-text articles written in English using the terms “postoperative ileus”, “treatment”, "etiology", and "pathophysiology". Papers published since 2008 combined with previous extensive reviews published up to 2009 were included, as were additional references from the author's files and studies on inflammation. Furthermore, we used the reference list of identified publications to select other relevant papers.

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