CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will take steps to limit the duration of ileus in their postoperative patients

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Current therapies to shorten postoperative ileus

ABSTRACT

Postoperative ileus delays hospital discharge, increases costs, and contributes to adverse outcomes. A variety of neural and chemical factors are involved. To shorten the duration of postoperative ileus, we may need to establish standard plans of care that favor earlier feeding, use of nasogastric tubes only on a selective basis, and prokinetic drugs as needed.

KEY POINTS

Postoperative ileus can selectively affect the stomach, small intestine, or large intestine, each with different causes and clinical presentation and each managed differently.

Laparoscopic surgery is associated with a shorter duration of postoperative ileus compared with open surgery.

Epidural anesthesia reduces the need for opiate analgesia after surgery and thus shortens the duration of postoperative ileus.

Drugs are being developed that block the effects of opiates on the gut while preserving their pain-relieving properties.

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RATHER THAN MERELY wait for bowel sounds to return after patients undergo surgery, we can try to get the gut working again sooner. An active approach might shorten the duration of postoperative ileus, allow patients to go home from the hospital sooner, and improve their outcomes.

In the pages that follow, we review the pathophysiology, diagnosis, and current therapies to alter the course of postoperative ileus.

ILEUS CAN AFFECT THE STOMACH OR SMALL OR LARGE INTESTINES

Ileus is the absence of intestinal peristalsis without mechanical obstruction; *postoperative ileus* refers to the time after surgery before coordinated electromotor bowel function resumes.

Although ileus classically refers to dysmotility of the small bowel, postoperative ileus can selectively affect the stomach, small intestine, or colon, each with a different mechanism and clinical presentation, and each managed differently (**TABLE 1**).

Gastroparesis refers to abnormal gastric motility leading to impaired gastric emptying. This disabling, potentially chronic condition is associated with certain medical conditions such as diabetes, but can also occur after some surgical procedures, as we will discuss. It has been estimated to affect approximately 4% of the adult population, with a strong female predilection.[1] Postoperative gastroparesis is probably most common after pancreaticoduodenectomy, in which it occurs in up to 57% of patients.[2] Consensus guidelines for grading the severity of gastroparesis have been devised to help standardize the reporting of outcomes.[2]

TABLE 1

Features of gastroparesis, small-bowel ileus, and colonic ileus

	SYMPTOMS	SIGNS	DIAGNOSIS	MANAGEMENT
Gastroparesis	Nausea +++ Vomiting +++ Abdominal pain +	Distention + Succussion splash	Abdominal x-ray [a] Gastric-emptying study	Nasogastric tube Metoclopramide (Reglan) Erythromycin Limit narcotics
Small-bowel ileus	Nausea ++ Vomiting ++ Abdominal pain +	Distention ++	Abdominal x-ray [a] Exclude small-bowel obstruction	Nasogastric tube Alvimopan (Entereg) Limit narcotics
Colonic ileus	Nausea + Vomiting + Abdominal pain +	Distention ++	Abdominal x-ray [a] Exclude colon obstruction	Neostigmine (Prostigmin) Decompressive colonoscopy Limit narcotics

+ = mild, ++ = moderate, +++ = severe

[a] Supine, kidney-ureter-bladder view

Normal times of ileus after surgery: small bowel, several hours; stomach, 24–48 hours; colon, 3–5 days

Acute colonic pseudo-obstruction (colonic ileus) is often seen in elderly hospitalized patients with multiple medical comorbidities. Of note, it often occurs after surgery to parts of the body other than the abdomen, such as after orthopedic procedures. One study documented an incidence of 1.3% after hip replacement surgery and 1.2% after spine procedures.[3]

The small bowel normally resumes activity several hours after surgery, the stomach 24 to 48 hours after surgery, and the colon 3 to 5 days after surgery.[4] When postoperative ileus persists longer than this, it can be considered pathologic and is sometimes called *paralytic ileus*.[4,5]

ILEUS AFFECTS OUTCOMES AND COSTS

Although not usually considered life-threatening, postoperative ileus is harmful for the patient and costly for society.

For the patient, ileus is uncomfortable, leads to nausea and vomiting, delays return to enteral nutrition, and prolongs the stay in the hospital. For many if not most patients undergoing gastrointestinal surgery, return of bowel function is the factor that delays going home. A prolonged hospital stay increases the risk of hospital-acquired infections, deep vein thrombosis, and other conditions.

The economic burden is also considerable. A retrospective review of more than 800,000 patients who underwent surgery in the United States in 2002 found a rate of postoperative ileus of 4.25% according to International Classification of Diseases–Ninth Revision (ICD-9) codes.[6] The mean hospital length of stay was 9.3 days in patients with postoperative ileus vs 5.3 days in those without it. The difference in mean total hospital costs was US $6,300 per patient. The costs certainly add up when you consider the number of surgical procedures performed every year.

NEURAL AND CHEMICAL FACTORS

While observing exteriorized bowel in 1872, Goltz[7] first noted enhanced spontaneous contractions when the spinal cord was severed at the level of the medulla. Not long after, Bayliss and Starling[8] used a device called an "enterograph" to monitor small-bowel activity in vivo in dogs and found that cutting the splanchnic nerves led to vigorous bowel contraction after laparotomy. These early observations formed the foundation of our understanding of postoperative ileus and some of its possible causes.

Normal bowel contractility is influenced by a host of neural and chemical factors, the relative contributions of which vary depending on the segment of bowel.

The *migrating motor complex* is the basal level of activity in the bowel in the fasting state, serving a "housekeeping" function.[9] It has four phases, consisting of escalating electrical and contractile activity punctuated by periods of quiescence. The resumption of this motor complex after surgery is responsible for recovery from postoperative ileus.

Sympathetic-parasympathetic imbalance

The sympathetic nervous system inhibits the small bowel; the parasympathetic nervous system stimulates it. Although vagal (parasympathetic) stimulation appears to have little actual impact on small-bowel activity, if sympathetic activity is blocked, contractility increases, indicating that tonic sympathetic inhibition normally predominates. The balance of these two competing influences determines the amount of acetylcholine released by excitatory nerve fibers in the myenteric plexi of the bowel.

These neural pathways can be manipulated clinically. Epidural catheters can block sympathetic output, thus allowing small-bowel function to return faster.

Vagus nerve activity appears to be more important in the stomach, where it promotes receptive relaxation of the fundus and contraction of the antrum, facilitating gastric emptying.[10] After vagotomy, emptying of liquids may be normal or accelerated, but emptying of solids is impaired. This can occur after peptic ulcer surgery but is more likely after gastric resection for malignancy or after inadvertent vagal nerve injury during antireflux surgery.

The enteric nervous system is a complex, intrinsic network of neurons consisting of two distinct plexi within the bowel wall: the submucosal (Meissner) plexus, and the myenteric (Auerbach) plexus.[11] The enteric nervous system in the small bowel is fundamentally different than the one in the colon in that the former contains gap junctions, allowing for coordinated electrical activity. Lacking these gap junctions, the colon depends more on input from the autonomic nervous system, perhaps explaining the longer recovery from postoperative ileus and the susceptibility to isolated colonic ileus due to a variety stressors and traumatic insults.[12]

Chemical mediators of bowel activity

A host of chemical mediators influence bowel motility. Perhaps the most important nonadrenergic inhibitor of gastrointestinal motility is nitric oxide.[13] Animal studies have firmly established nitric oxide as an important factor in postoperative ileus, but its exact role in humans is not clear.[14,15]

Other mediators with possible roles include vasoactive intestinal peptide, substance P, calcitonin gene-related peptide, and endogenous opioids.[13] Lack of duodenal-derived motilin is thought to be one cause of delayed gastric emptying after pancreaticoduodenectomy.[2]

Inflammation

The inflammatory response after surgery has also been an attractive target of study of the factors promoting postoperative ileus. In rat studies, Kalff et al[16] found that surgical manipulation of the bowel induced an inflammatory cellular infiltrate in the bowel wall and diminished the response of smooth muscle to cholinergic stimulation. Cyclooxygenase-2, the enzymatic precursor to prostaglandins, has also been shown to be induced in enteric neurons after laparotomy.[17]

Narcotic analgesics

One of the greatest hurdles in preventing postoperative ileus is the use of narcotic analgesics to treat postoperative pain. It is also one of the most important modifiable risk factors.

Opiates are a modifiable risk factor for postoperative ileus

Opiates delay colonic transit in postoperative patients, an effect that can be reversed by the narcotic antagonist naloxone (Narcan).[18] This inhibitory effect is mediated by peripheral mu-opioid receptors. In a study of patients undergoing colectomy, the more morphine given, the longer the time to the return of bowel sounds and flatus and the first bowel movement.[19]

These observations have led to a search for selective opiate antagonists that allow narcotics to continue relieving pain while counteracting their effect on bowel motility, a topic discussed later in this review.

Nonsteroidal anti-inflammatory drugs such as ketorolac (Toradol) are attractive alternatives to opiate analgesics, both for their anti-inflammatory effect and for their opiate-sparing properties. However, they can cause

bleeding, renal insufficiency, and gastritis, drawbacks that limit their applicability and duration of use.

DIAGNOSIS BY CLINICAL SUSPICION AND IMAGING

The diagnosis of postoperative ileus is driven by a combination of clinical suspicion and imaging tests.

Regardless of the segment of bowel involved, it is imperative to exclude an obstructive cause. The diagnosis of ileus is presumed once obstruction has been excluded.

Diagnosing gastroparesis

Postoperative gastroparesis is usually suspected by its symptoms of early satiety, nausea, vomiting, eructation, and gastroesophageal reflux. Abdominal distention is usually not a prominent sign, but a succussion splash may be detected, indicating retention of food and liquid in the stomach.

Plain radiographs may reveal a large gastric air bubble in the left upper quadrant but may underestimate the degree of gastric distention. Computed tomography (CT) may show a large, fluid-filled stomach, often containing high-density food debris.

Excluding an obstructive cause of ileus is imperative

The gold standard for diagnosis is gastric emptying scintigraphy after a radiolabelled solid meal. The patient consumes a meal of egg white labelled with technetium 99m sulfur colloid, and scanning is performed at specified intervals to measure the percent retention of the isotope. Retention of more than 10% at 4 hours is considered abnormal.[1] Severity can be graded on the basis of percent retention after 4 hours.[20]

This test is rarely indicated in the acute postoperative setting, however, and patients should be treated presumptively to prevent aspiration once mechanical obstruction is excluded.

Diagnosing small-bowel ileus

Small-bowel ileus often presents like gastroparesis, except that it more often causes abdominal distention. Plain radiographs reveal air-fluid levels and dilated loops of bowel.

Small-bowel ileus must then be differentiated from small-bowel obstruction by clinical and radiographic features. The presence of crampy abdominal pain, bowel sounds, and some bowel function implies a degree of mechanical obstruction. Plain radiographs showing "step-ladder" air-fluid levels also suggest obstruction. CT is more definitive in diagnosing obstruction by the presence of distended and decompressed bowel loops and may also reveal a source of obstruction (eg, postoperative interloop abscess).

Diagnosing colonic ileus

Colonic ileus is also characterized by abdominal distention, sometimes marked. Although it is the colon that is primarily involved, upstream small-bowel dilatation can also be seen if the ileocecal valve is incompetent. The cecum often shows the greatest degree of dilatation on plain radiographs and is at the greatest risk of perforation. CT, contrast enema studies, and endoscopy help rule out mechanical obstruction due to volvulus or a mass lesion.

STRATEGIES TO PREVENT AND TREAT ILEUS

Many strategies have been applied to prevent and manage postoperative ileus, ranging from changes in surgical technique, supportive care, and patient-initiated activities, to pharmacologic intervention.

Epidural anesthesia shortens ileus, reduces the need for narcotics

Epidural anesthesia has shown promise not only in improving pain control, but also in shortening the period of postoperative ileus. Most surgical patients either receive an epidural catheter before surgery, which is left in place for postoperative pain control, or are given patient-controlled analgesia with a narcotic. Generally, the surgeon chooses the pain control method.

Thoracic epidural analgesia has been shown to hasten the return of bowel function by 1 to 2 days and to reduce the need for opiates compared with systemic opioids alone.[21–26] A likely explanation is that epidural anesthesia interferes with the afferent and efferent sympathetic reflex arcs. The level of the epidural placement is important: a thoracic epidural is needed to effectively block these sympathetic pathways.

Laparoscopic surgery is less traumatic

Laparoscopy has changed the landscape of surgery over the past few decades. Some of the most common surgical procedures (appendectomy, cholecystectomy) are now done mainly via the laparoscope, as are many procedures that are more complex.

Laparoscopic surgery has several advantages over open surgery. With smaller incisions, it is less traumatic to the body. The systemic inflammatory response appears to be less vigorous after laparoscopic surgery than after open surgery, as measured by circulating levels of interleukin 1, interleukin 6, and C-reactive protein.[27]

The length of stay after a laparoscopic procedure is shorter than after an open procedure for several reasons, not the least of which is a shorter duration of postoperative ileus. Animal studies show that intestinal recovery is faster after laparoscopic procedures than after open procedures.[28–30] In a study in which their other care was comparable, significantly fewer patients undergoing laparoscopic colectomy had emesis or needed their nasogastric tube to be reinserted than patients who underwent an open operation, and their length of stay was shorter.[31]

As technology continues to advance in minimally invasive surgery, it is reasonable to expect these trends to continue.

Nasogastric tubes in selected cases

Patients are often allowed nothing by mouth or only minimal oral intake immediately after abdominal surgery, with or without nasogastric decompression. The role of nasogastric decompression has long been a topic of controversy. In a meta-analysis of 26 trials with 3,964 patients, the groups in which all patients routinely received a nasogastric tube had higher rates of pneumonia, fever, and atelectasis and longer duration to resumption of oral feeding than the groups in which nasogastric tubes were used selectively.[32]

Most clinicians agree that nasogastric tubes are uncomfortable and do little to prevent postoperative ileus. However, in selected cases they are useful for managing intractable vomiting and for preventing aspiration of gastric contents.

Early enteral feeding

Evidence is mounting that early postoperative enteral feeding may be advantageous for recovery.

In 1,173 patients undergoing both upper and lower gastrointestinal surgery in 13 trials, fewer patients died who were randomized to receive enteral feeding within 24 hours.[33] There were also fewer infectious complications and anastomotic problems and a shorter length of stay, but these differences were not statistically significant. Vomiting was more common in the early-feeding groups but did not lead to higher rates of morbidity. Enteral feeding was by the oral, nasoduodenal, or nasojejunal routes, depending on the type of surgery performed.

Whether the number of calories given affects the outcome remains to be clarified, but at least for now it seems that feeding patients early in the course of their recovery is not detrimental and may in fact be beneficial.

Gum-chewing

Gum-chewing has been studied over the last decade as a form of sham feeding to stimulate bowel recovery after surgery. The presumed mechanism of action is vagal cholinergic (parasympathetic) stimulation of the gastrointestinal tract, similar to oral intake but with theoretically less risk of vomiting and aspiration.

In five such trials in patients undergoing colon resection, gum-chewing shortened the time until first flatus and bowel movement, but made no significant difference in length of stay.[34]

At the very least, gum-chewing immediately after surgery is a cheap and harmless strategy for reducing postoperative ileus, and it might make the patient more comfortable.

Nasogastric tubes are uncomfortable and do little to prevent postoperative ileus

DRUGS THAT COAX THE GUT BACK TO WORK

Drugs that coax the gastrointestinal tract back to work have been tried for many years and have recently gained renewed enthusiasm. Their efficacy varies according to their target organ, with greater success in the stomach and colon than in the small bowel.

Cisapride (Propulsid) was an effective gas-

tric prokinetic agent, as shown in several controlled trials. However, it was withdrawn from the US market in 2000 because of its propensity to cause cardiac arrhythmias.

Erythromycin is a macrolide antibiotic that is also a motilin receptor agonist. In patients who underwent antrectomy and vagotomy, it was shown to accelerate gastric emptying by roughly 40% as measured by solid-phase gastric emptying scintigraphy.[35,36] In a randomized controlled trial in 118 patients who underwent pancreaticoduodenectomy, intravenous erythromycin reduced gastroparesis by 37% (measured by solid-phase gastric emptying study) and also reduced the need for nasogastric tube reinsertion.[37] A major shortcoming is the development of tachyphylaxis, thought to be mediated by down-regulation of motilin receptors.

Metoclopramide (Reglan) is an antiemetic and prokinetic that acts as a dopamine D2 receptor antagonist and mixed serotonin 5-HT3 antagonist/5-HT4 agonist. Metoclopramide also stimulates gastric emptying, as shown in controlled trials in patients in intensive care units.[38,39] The drug should not be used in patients with parkinsonism, in view of its antidopamine properties.

Earlier feeding after surgery does no harm, and may even help

In 2009, the US Food and Drug Administration required that a black box warning be added to metoclopramide because of the risk of tardive dyskinesia with long-term use, and recommended that its use be limited to 3 weeks in the acute setting.[40] Prescribers and patients need to decide if this risk is worth the potential benefit on a case-by-case basis.

Although erythromycin and metoclopramide are effective in managing gastroparesis, neither has been shown to be effective for small-bowel ileus.[41,42] However, colonic ileus is highly responsive to drug therapy.

Neostigmine (Prostigmin) is a reversible acetylcholinesterase inhibitor that enhances the activity of the neurotransmitter acetylcholine at muscarinic receptors. It is the first-line treatment for colonic ileus.[43] In three randomized, placebo-controlled trials,[44–46] the success rates were 85% to 94% after the first dose.

Neostigmine is generally given either as an intravenous bolus dose of 2 to 2.5 mg or as an intravenous infusion over 24 hours. It must be given in a monitored setting, as both bradycardia and bronchospasm can occur. Patients should continue to be monitored clinically and with plain abdominal radiography after the drug is given, and they sometimes require a second or third dose.

In cases in which neostigmine fails, decompressive colonoscopy can be done as a second-line measure.

Alvimopan (Entereg), a peripherally acting, mu-opioid receptor antagonist, has come on the scene most recently. This agent first showed promise when it precipitated diarrhea in morphine-dependent mice.[47] Early studies in humans focused on its ability to reverse the effect of opiates on gastrointestinal transit without interfering with their analgesic properties.[48–50] Later investigations concentrated on its ability to reduce the duration of postoperative ileus after a variety of major abdominal surgical procedures.[51,52]

A pooled analysis of phase III studies of alvimopan focused on the subset of 1,212 patients who underwent bowel resections; it found a significant reduction in the time to gastrointestinal tract recovery and hospital discharge.[53] A 12-mg dose was more beneficial than a 6-mg dose, especially in females and in older patients (over age 65).

Most recently, a multicenter, double-blind, placebo-controlled trial evaluated alvimopan as part of a standardized postoperative care plan in 654 patients undergoing partial small-bowel and large-bowel resection.[54] The alvimopan group took less time to have their first bowel movements, pass flatus, and tolerate solid food. Patients randomized to alvimopan also had their discharge orders written an average of 1 day sooner than the placebo group. Importantly, opioid use was the same in both groups.

Alvimopan is given as a single oral dose of 12 mg 30 to 90 minutes before surgery and twice daily after surgery for up to 7 days, for a total of 15 doses. It is contraindicated in patients receiving therapeutic doses of opiates for more than 7 consecutive days immediately before surgery. Its use is currently limited to hospitals enrolled in the EASE (Entereg Access Support and Education) program.

Common adverse effects include constipation, dyspepsia, flatulence, and urinary retention. In a placebo-controlled 12-month study

in patients treated with opiates for chronic pain, there were more reports of myocardial infarction in the alvimopan group.[55] This finding has not been replicated in any other study. The need to give the drug preoperatively obviously necessitates identifying patients most at risk of postoperative ileus.

FUTURE DIRECTIONS

A multimodal approach to managing postoperative ileus seems likely to be the most effective model in the long run. This should involve using minimally invasive surgery when possible, pharmacotherapy, and accelerated standardized postoperative care.

Standardized postoperative care has been implemented for a variety of procedures and generally involves minimal (if any) use of nasogastric tubes, early enteral intake and ambulation, and specific discharge criteria such as passage of flatus or stool, adequate pain control, and tolerance of solid food.[56–58] Compared with a "traditional" (nonstandardized) approach, standardized care has led to shorter hospital stays and lower costs with no impact on rates of morbidity or readmission.[59,60] (However, one clearly cannot underestimate the role of patient expectations in the success of such postoperative care pathways.)

There are plenty of incentives for patients, physicians, health care organizations, and third-party payers to support this push. For patients, it means less time in the hospital and a quicker return to eating normally. Surgeons can expect more-satisfied patients and lower rates of hospital-acquired conditions. For hospitals and insurers, it means less use of resources for some patients, making resources available to those who need them more.

REFERENCES

1. **Waseem S, Moshiree B, Draganov P**. Gastroparesis: current diagnostic challenges and management considerations. World J Gastroenterol 2009; 15:25–37.
2. **Wente MN, Bassi C, Dervenis C, et al**. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142:761–768.
3. **Norwood MG, Lykostratis H, Garcea G, Berry DP**. Acute colonic pseudo-obstruction following major orthopaedic surgery. Colorectal Dis 2005; 7:496-499.
4. **Livingston EH, Passaro EP**. Postoperative ileus. Dig Dis Sci 1990; 35:121–132.
5. **Catchpole BN**. Ileus: use of sympathetic blocking agents in its treatment. Surgery 1969; 66:811–820.
6. **Saunders WB, Bowers B, Moss B, et al**. Recorded rate and economic burden associated with postoperative ileus [abstract]. Presented at the ASHP Midyear Clinical Meeting, Orlando, FL, December 7, 2004. Abstract 30346.
7. **Neely J, Catchpole BN**. The restoration of alimentary-tract motility by pharmacological means. Br J Surg 1971; 58:21–28.
8. **Bayliss WM, Starling EH**. The movements and innervations of the small intestine. J Physiol 1899; 24:99–143.
9. **Szurszewksi JH**. A migrating electrical complex of the canine small intestine. Am J Physiol 1969; 217:1757–1763.
10. **Livingston EH**. Stomach and duodenum. In: Norton JA, Bollinger RR, Chang AE, et al (editors). Surgery: Basic Science and Clinical Evidence. New York, Springer-Verlag, 2001:489–516.
11. **Simeone DM**. Anatomy and physiology of the small intestine. In: Mulholland MW, Lillemoe KD, Doherty GM, Maier RV, Upchurch GR, editors. Greenfield's Surgery: Scientific Principles and Practice, 4th ed. Philadelphia: Lippincott Williams and Wilkins, 2006:756–766.
12. **Baig MK, Wexner SD**. Postoperative ileus: a review. Dis Colon Rectum 2004; 47:516–526. Retraction in Dis Colon Rectum 2005; 48:1983.
13. **Luckey A, Livingston E, Taché Y**. Mechanisms and treatment of postoperative ileus. Arch Surg 2003; 138:206–214.
14. **De Winter BY, Boeckxstaens GE, De Man JG, Moreels TG, Herman AG, Pelckmans PA**. Effect of adrenergic and nitrergic blockade on experimental ileus in rats. Br J Pharmacol 1997; 120:464–468.
15. **Kalff JC, Schraut WH, Billiar TR, Simmons RL, Bauer AJ**. Role of inducible nitric oxide synthase in postoperative intestinal smooth muscle dysfunction in rodents. Gastroenterology 2000; 118:316–327.
16. **Kalff JC, Schraut WH, Simmons RL, Bauer AJ**. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg 1998; 228:652–663.
17. **Schwarz NT, Kalff JC, Türler A, et al**. Prostanoid production via COX-2 as a causative mechanism of rodent postoperative ileus. Gastroenterology 2001; 121:1354–1371.
18. **Kaufman PN, Krevsky B, Malmud LS, et al**. Role of opiate receptors in the regulation of colonic transit. Gastroenterology 1988; 94:1351–1356.
19. **Cali RL, Meade PG, Swanson MS, Freeman C**. Effect of morphine and incision length on bowel function after colectomy. Dis Colon Rectum 2000; 43:163–168.
20. **Abell TL, Camilleri M, Donahoe K, et al; American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine**. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am J Gastroenterol 2008; 103:753–763.
21. **Zingg U, Miskovic D, Hamel CT, Erni L, Oertli D, Metzger U**. Influence of thoracic epidural analgesia on postoperative pain relief and ileus after laparoscopic colorectal resection: benefit with epidural analgesia. Surg Endosc 2009; 23:276–282.
22. **Taqi A, Hong X, Mistraletti G, Stein B, Charlebois P, Carli F**. Thoracic epidural analgesia facilitates the restoration of bowel function and dietary intake in patients undergoing laparoscopic colon resection using a traditional, nonaccelerated, perioperative care program. Surg Endosc 2007; 21:247–252.
23. **Kuo CP, Jao SW, Chen KM, et al**. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain, and bowel function in patients undergoing colonic surgery. Br J Anaesth 2006; 97:640–646.
24. **Carli F, Trudel JL, Belliveau P**. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. Dis Colon Rectum 2001; 44:1083–1089.
25. **Jørgensen H, Wetterslev J, Møiniche S, Dahl JB**. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery.

Cochrane Database Syst Rev 2000; 4:CD001893.
26. **de Leon-Casasola OA, Karabella D, Lema MJ**. Bowel function recovery after radical hysterectomies: thoracic epidural bupivacaine-morphine versus intravenous patient-controlled analgesia with morphine: a pilot study. J Clin Anesth 1996; 8:87–92.
27. **Leung KL, Lai PB, Ho RL, et al**. Systemic cytokine response after laparoscopic-assisted resection of rectosigmoid carcinoma: a prospective randomized trial. Ann Surg 2000; 231:506–511.
28. **Böhm B, Milsom JW, Fazio VW**. Postoperative intestinal motility following conventional and laparoscopic intestinal surgery. Arch Surg 1995; 130:415–419.
29. **Davies W, Kollmorgen CF, Tu QM, et al**. Laparoscopic colectomy shortens postoperative ileus in a canine model. Surgery 1997; 121:550–555.
30. **Hotokezaka M, Combs MJ, Mentis EP, Schirmer BD**. Recovery of fasted and fed gastrointestinal motility after open versus laparoscopic cholecystectomy in dogs. Ann Surg 1996; 223:413–419.
31. **Chen HH, Wexner SD, Iroatulam AJ, et al**. Laparoscopic colectomy compares favorably with colectomy by laparotomy for reduction of postoperative ileus. Dis Colon Rectum 2000; 43:61–65.
32. **Cheatham ML, Chapman WC, Key SP, Sawyers JL**. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg 1995; 221:469–478.
33. **Lewis SJ, Andersen HK, Thomas S**. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg 2009; 13:569–575.
34. **Purkayastha S, Tilney HS, Darzy AW, Tekkis PP**. Meta-analysis of studies evaluating chewing gum to enhance postoperative recovery following colectomy. Arch Surg 2008; 143:788–793.
35. **Ramirez B, Eaker EY, Drane WE, Hocking MP, Sninsky CA**. Erythromycin enhances gastric emptying in patients with gastroparesis after vagotomy and antrectomy. Dig Dis Sci 1994; 39:2295–2300.
36. **Kendall BJ, Chakravarti A, Kendall E, Soykan I, McCallum RW**. The effect of intravenous erythromycin on solid meal gastric emptying in patients with chronic symptomatic post-vagotomy-antrectomy gastroparesis. Aliment Pharmacol Ther 1997; 11:381–385.
37. **Yeo CJ, Barry MK, Sauter PK, et al**. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. Ann Surg 1993; 218:229–237.
38. **Jooste CA, Mustoe J, Collee G**. Metoclopramide improves gastric motility in critically ill patients. Intensive Care Med 1999; 25:464–468.
39. **Sustic A, Zelic M, Protic A, et al**. Metoclopramide improves gastric but not gallbladder emptying in cardiac surgery patients with early intragastric enteral feeding: randomized controlled trial. Croat Med J 2005; 46:239–244.
40. **US Food and Drug Administration.** FDA requires boxed warning and risk mitigation strategy for metoclopramide-containing drugs. Agency warns against chronic use of these products to treat gastrointestinal disorders. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149533.htm. Accessed 8/24/2009.
41. **Smith AJ, Nissan A, Lanouette NM, et al**. Prokinetic affect of erythromycin after colorectal surgery: a randomized, placebo-controlled, double-blind study. Dis Colon Rectum 2000; 43:333–337.
42. **Cheape JD, Wexner SD, Jagelman JK**. Does metoclopramide reduce the length of ileus after colorectal surgery? A prospective randomized trial. Dis Colon Rectum 1991; 34:437–441.
43. **De Giorgio R, Knowles CH**. Acute colonic pseudo-obstruction. Br J Surg 2009; 96:229–239.
44. **Ponec RJ, Saunders MD, Kimmey MB**. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 1999; 341:137–141.
45. **Amaro R, Rogers AI**. Neostigmine infusions: new standard of care for acute colonic pseudo-obstruction? Am J Gastroenterol 2000; 95:304–305.
46. **van der Spoel JI, Oudemans-van Straaten HM, Stroutenbeek CP, Bosman RJ, Zandstra DF**. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure: a prospective, double-blind, placebo-controlled trial. Intensive Care Med 2001; 27:822–827.
47. **Zimmerman DM, Gidda JS, Cantrell BE, et al**. LY246736 dihydrate μ-opioid receptor antagonist. Drugs Future 1994; 19:1078–1083.
48. **Callaghan JT, Cerimele B, Nowak TV, et al**. Effect of the opioid antagonist LY246736 on gastrointestinal transit in human subjects [abstract]. Gastroenterology 1998; 114:G3015.
49. **Hodgson PS, Liu SS, Carpenter RI**. ADL 8-2698 prevents morphine inhibition of GI transit [abstract]. Clin Pharmacol Ther 2000; 67:93.
50. **Liu SS, Hodgson PS, Carpenter RL, Fricke JR Jr**. ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, prevents gastrointestinal effects of intravenous morphine without affecting analgesia. Clin Pharmacol Ther 2001; 68:66–71.
51. **Wolff BG, Michelassi F, Gerkin TM, et al**. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 2004; 240:728–735.
52. **Delaney CP, Weese JL, Hyman NH, et al; Alvimopan Postoperative Ileus Study Group**. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum 2005; 48:1114–1129.
53. **Delaney CP, Wolff BG, Viscusi ER, et al**. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. Ann Surg 2007; 245:355–363.
54. **Ludwig K, Enker WE, Delaney CP, et al**. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg 2008; 143:1098–1105.
55. **Adolor GlaxoSmithKline**. Entereg (alvimopan). www.entereg.com/ Accessed 8/24/2009.
56. **Pritts TA, Nussbaum MS, Flesch LV, Fegelman EJ, Parikh AA, Fischer JE**. Implementation of a clinical pathway decreases length of stay and cost for bowel resection. Ann Surg 1999; 230:728–733.
57. **Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW**. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 2003; 46:851–859.
58. **Joh YG, Lindsetmo RO, Stulberg J, Obias V, Champagne B, Delaney CP**. Standardized postoperative pathway: accelerating recovery after ileostomy closure. Dis Colon Rectum 2008; 51:1786–1789.
59. **Kennedy EP, Rosato EL, Sauter PK, et al**. Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution—the first step in multidisciplinary team building. J Am Coll Surg 2007; 204:917–924.
60. **Kariv Y, Delaney CP, Senagore AJ, et al**. Clinical outcomes and cost analysis of a "fast track" postoperative care pathway for ileal pouch-anal anastomosis: a case control study. Dis Colon Rectum 2007; 50:137–146.

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