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Gastrointestinal dysmotility disorders in critically ill dogs and cats

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Abstract

Objective – To review the human and veterinary literature regarding gastrointestinal (GI) dysmotility disorders in respect to pathogenesis, patient risk factors, and treatment options in critically ill dogs and cats.
Etiology – GI dysmotility is a common sequela of critical illness in people and small animals. The most common GI motility disorders in critically ill people and small animals include esophageal dysmotility, delayed gastric emptying, functional intestinal obstruction (ie, ileus), and colonic motility abnormalities. Medical conditions associated with the highest risk of GI dysmotility include mechanical ventilation, sepsis, shock, trauma, systemic inflammatory response syndrome, and multiple organ failure. The incidence and pathophysiology of GI dysmotility in critically ill small animals is incompletely understood.
Diagnosis – A presumptive diagnosis of GI dysmotility is often made in high-risk patient populations following detection of persistent regurgitation, vomiting, lack of tolerance of enteral nutrition, abdominal pain, and constipation. Definitive diagnosis is established via radioscintigraphy; however, this diagnostic tool is not readily available and is difficult to perform on small animals. Other diagnostic modalities that have been evaluated include abdominal ultrasonography, radiographic contrast, and tracer studies.
Therapy – Therapy is centered at optimizing GI perfusion, enhancement of GI motility, and early enteral nutrition. Pharmacological interventions are instituted to promote gastric emptying and effective intestinal motility and prevention of complications. Promotility agents, including ranitidine/nizatidine, metoclopramide, erythromycin, and cisapride are the mainstays of therapy in small animals.
Prognosis – The development of complications related to GI dysmotility (eg, gastroesophageal reflux and aspiration) have been associated with increased mortality risk. Institution of prophylaxic therapy is recommended in high-risk patients, however, no consensus exists regarding optimal timing of initiating prophylaxic measures, preference of treatment, or duration of therapy. The prognosis for affected small animal patients remains unknown.

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Keywords: delayed gastric emptying, enteral feeding, gastrointestinal stasis, hypomotility, ileus

Abbreviations

5HT	5-hydroxytryptamine; serotonin
Ach	acetylcholine
CCK	cholecystokinin
CNS	central nervous system
CRI	constant rate infusion
EN	enteral nutrition
ENS	enteric nervous system
GI	gastrointestinal
GIDM	gastrointestinal dysmotility
GRV	gastric residual volume
IAP	intra-abdominal pressure
LES	lower esophageal sphincter
MMC	migrating motor complex
NO	nitric oxide
SIRS	systemic inflammatory response syndrome
VIP	vasoactive intestinal peptide

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Introduction

Gastrointestinal (GI) motility is a coordinated process integrating myoelectrical activity, contractile activity, tone, compliance, and transit.[1] Functions of normal GI motility include propelling ingesta forward, retaining ingesta at a given site for absorption, and physically breaking down and circulating ingesta for digestion.[2] The GI tract is a target organ for injury in critically ill patients, and GI

motility has been shown to be directly affected by systemic derangements. Abnormal GI motility or GI dysmotility (GIDM) is a common complication in critically ill people,[3,4] and it has been characterized by inhibition of forward GI motility, and less frequently, hypermotility.[4] The most common GI motility disorders in critically ill human and small animal veterinary patients include esophageal dysmotility, delayed gastric emptying, functional intestinal obstruction (ie, ileus), and colonic motility abnormalities.[5,6]

The exact incidence and frequency of GIDM in critically ill dogs and cats has not been clearly defined. The same risk factors for GIDM in people (eg, mechanical ventilation, sepsis, shock, trauma, systemic inflammatory response syndrome [SIRS], and multiple organ failure), also occur in critically ill dogs and cats. GIDM is an important component of the management of the critically dogs and cats, and improving our understanding of GIDM is crucial for effective prophylaxis and treatment considerations.

Review of normal GI physiology

Nervous control of GI motility is a complex and coordinated process that includes contractile activity, tone, compliance, myoelectric stimulation, and movement of substances through the GI tract. These processes are generated and modulated by neurohumoral factors via stimulation of both the enteric and central nervous systems (ENS and CNS).[2,4,7] Motor neurons in the GI wall respond similarly across many species and are excited by substances such as acetylcholine (Ach),[8] tachykinins (particularly substance P and neurokinin A),[9,10] and serotonin (5-hydroxytryptamine [5-HT]),[11,12] and inhibited by peptides, including vasoactive intestinal peptide (VIP),[13] somatostatin,[14] nitric oxide (NO),[15] and gamma-amino butyric acid (GABA).[12] Parasympathetic innervation, mainly via the vagus and pelvic nerves, integrates with input from other preganglionic parasympathetic fibers (eg, afferent neurons, interneurons of the enteric system) to supply innervation to the GI tract with Ach as the primary neurotransmitter. Sympathetic innervation consists of mainly norepinephrine as the major neurotransmitter and acts indirectly on neurons of the enteric system and directly on muscles and glands. Downregulation of inhibitory neurons could lead to GI hypermotility, while impaired excitatory function could lead to GI hypomotility such as ileus and delayed gastric emptying.

Movement patterns of the gut can be divided into either interdigestive motility patterns or digestive motility patterns. Interdigestive motility is characterized by the interdigestive motility complex, an alternate form of motility that clears indigestible material and includes the migrating motor complex (MMC). This complex, often referred to as the "housekeeping" function, involves pyloric relaxation while a strong wave of peristalsis moves over the antrum, forcing less digestible material into the duodenum aborally.[16] Regulation of the MMC is achieved by the ENS and modulated directly by regulatory peptides including somatostatin,[17] motilin,[18] and pancreatic polypeptide.[19] MMCs, which occur at a rate of 15–20 contractions per minute in dogs, may play an important role in defending against bacterial overgrowth of particles remaining in the bowel.[20,21] It is important to note that cats do not generate MMCs in the fasting state, but feline interdigestive motility is characterized by giant migrating complexes.[5] In intermittent feeders, ingestion of a meal interrupts the interdigestive motility pattern, and a digestive motility pattern begins in various anatomic locations of the GI tract.[22] The MMC is then replaced by the fed pattern of activity, or digestive motility, which consists of accommodation, stationary motility, and propulsive peristalsis.[7]

Esophageal motility is controlled via different mechanisms in both the smooth and striated muscle of the esophagus.[23] Canine esophagus is made entirely of striated skeletal muscle, whereas feline esophagus has a distal portion that is smooth muscle. Striated skeletal muscle fibers are regulated by somatic motor neurons of the vagus nerve, whereas smooth muscle fibers are regulated by the ENS and are indirectly controlled by the autonomic nervous system. The lower esophageal sphincter (LES) maintains control of the bolus of food that enters the stomach, while peristaltic contraction propels the food bolus into the stomach.[1] Neurohormonal control of esophageal motility is poorly characterized, but several hormonal influences have been described, including NO,[24] somatostatin,[25] and motilin.[26]

Gastric motility is a highly coordinated process including adaptive and receptive relaxation followed by emptying of contents into the duodenum. Receptive relaxation of the stomach, which occurs during chewing and swallowing, is brief and is regulated by a vagovagal reflex. Adaptive relaxation is characterized by relaxation of the muscles as the food enters the stomach, which allows retention of large quantities of food and minimizes pressure changes as food volume increases. The inhibitory vagal fibers stimulated by adaptive relaxation release Ach and activate inhibitory enteric pathways, releasing NO, VIP, or ATP and causing muscle relaxation.[15,27] Reflex or feedback regulation is induced by nutrients and neurohormones of the small intestine to begin coordination of gastric emptying.

Gastric emptying is a tightly controlled process that requires the coordination of multiple factors, including relaxation of the fundal portion of the stomach, activation of antral peristalsis, opening of the pyloric

diameter, relaxation of the duodenum, and contraction of the duodenum.[28] Motility of the stomach can be stimulated by hormones or drugs; however, gastric emptying can only occur when the coordination among the fundus, gastric pump, antrum, and duodenum is preserved. Afferent receptors in the duodenum that send feedback signals to the stomach are activated by a low pH, high osmolality, and the presence of high lipid content.[27,29] The "enterogastric reflex" inhibits the vagal nuclei of the medulla and local reflexes while activating sympathetic fibers that cause the pyloric sphincter to tighten, delaying gastric emptying.[30]

In contrast to the stomach, there are 5 main contractile patterns in the small intestine: peristaltic waves, stationary segmenting contractions, giant contractions (aboral), stationary or migrating clusters of contractions, and MMCs.[2] Propagation velocities of peristaltic waves lead to an average small intestinal transit time of 3–5 hours in healthy dogs[31] and 2–3 hours in healthy cats.[32] All of these motility patterns are affected by various neurohumoral factors and can become dysregulated in pathologic states. Colonic motility consists of short duration phasic contractions amidst a background state of persistent colonic tone.[33–35]

GIDM in critical illness

GIDM is a common sequelae of critical illness in both people and small animals. Delayed transit disorders are the most common motility disorders in critically ill dogs and cats, and these disorders may involve the esophagus (eg, hypomotility, megaesophagus), stomach (ie, delayed gastric emptying), small intestine (ie, functional ileus), and colon (ie, constipation).[5] Common complications in patients with GIDM include aspiration pneumonia,[36,37] esophagitis, feeding difficulties,[3] increased risk of bacterial translocation and sepsis,[38,39] and increased intra-abdominal pressure (IAP).[40]

Pathophysiology of GIDM

Esophageal motility disturbances are frequently observed in critically ill patients. In mechanically ventilated patients, the frequency, amplitude, and percentage of propulsive contractions of the esophagus are reduced.[41] The most clinically significant sequelae of changes in esophageal motor activity are the development of gastroesophageal reflux due to relaxation of the LES. Changes in esophageal motor activity and decreases in the pressure of the LES result in regurgitation of gastric contents, esophagitis, and subsequent aspiration.[42] Several medications used during mechanical ventilation, such as ketamine, benzodiazepines, and opioids, have also been associated with inhibition of esophageal motor activity.[41]

Delayed gastric emptying, or gastric stasis, has been associated with many diseases in veterinary patients, including both primary and secondary disorders. Delayed gastric emptying is a functional disorder caused by defects in myenteric neuronal and gastric smooth muscle function leading to impaired emptying of digesta from the stomach. The term "gastroparesis" has been used historically to describe this phenomenon, but is no longer considered specific enough to account for all motor impairments that occur in gastric stasis. The pathophysiology of delayed gastric emptying in critically ill human and small animal patients has not been fully elucidated; however, several theories exist. One hypothesis suggests that delayed gastric emptying is the result of a primary motor dysfunction ("pump failure"), leading to decreased antral motility and display of the fasting motility pattern during feeding.[43] Another hypothesis describes the disproportionate activation of an inhibitory feedback pathway originating in the proximal small intestine or duodenum ("excessive feedback").[44] The "excessive feedback theory" is based on the nutrient release of neuroendocrine peptides such as cholecystokinin (CCK) and 5-HT (via 5-HT3 receptors), which subsequently inhibit vagal and spinal afferent neurons and result in delayed gastric emptying. This theory has been recently supported by the finding of increased fasting and nutrient-stimulated plasma CCK concentrations in critically ill human patients with delayed gastric emptying.[45]

Ileus is characterized by lack of borborygmi, accumulation of gas and fluid in the bowel with subsequent abdominal distension, and decreased advancement of GI contents.[5] A functional ileus occurs commonly in critically ill patients.[40] A recent hypothesis suggests a loss of synchronized coordination and dysfunctional peristalsis as a cause of ileus in critically ill patients.[28] This hypothesis contests the previous idea that paralysis and decreased motor activity in the muscularis portion of the GI tract predominates during ileus. Inflammatory mediators have also been implicated in the pathophysiology of ileus. During GI inflammation, leukocytes (particularly neutrophils) may damage the muscle layer of the GI tract directly by releasing proteolytic enzymes and cytokines.[46] The release of these inflammatory mediators leads to release of NO, paralysis of the muscular cells, and ultimately, propagation of intestinal dilation. This relationship between NO and intestinal dilation has driven the recent development of NO synthase inhibitors.

Disturbances in the interdigestive motility pattern have contributed to delayed small bowel transit. One human study reported that postoperative MMCs in critically ill people differed from those in control subjects

due to observed increase in phase I, less phase II, and more frequent phase III activity.[47] The peristaltic contractions of phase III tend to be retrograde and thus significantly delay small bowel transit. MMC disturbances reduce expelling of the luminal contents, including bacteria and food particles, into the colon, and they may result in microbial overgrowth and possibly subsequent bacterial translocation. The failure of motor activity to transition between an interdigestive and a digestive pattern may contribute to the occurrence of diarrhea or the persistence of ileus in critically ill human and veterinary patients.[48]

The colons of critically ill patients present a variety of motility disturbances, including constipation and megacolon or decreased colonic tone. In idiopathic constipation, patients often have delayed clearance of the ascending and transverse colon and longer colonic transit times.[49] Decreased colonic motility may be mediated through extrinsic neural pathways resulting in a viscera-visceral reflex inhibition, or from a combined derangement with associated colonic motor dysfunction.[50]

Megacolon can be seen in critically ill small animal veterinary patients and is associated with decreased colonic tone; however, phasic contractility of the dilated segment is usually normal. In human medicine, this acute colonic pseudo-obstruction is known as Ogilvie's syndrome, and it has been associated with gut ischemia, systemic or local inflammation, and sepsis. Ogilvie's syndrome is affiliated with an autonomic imbalance, an impaired pelvic parasympathetic innervation, and a predominance of inhibitory sympathetic tone.[51,52] Rates of functional colonic pseudo-obstruction in critically ill small animal veterinary patients have not been reported. Megacolon in cats occurs with greater frequency than in dog,[53] however, this end-stage condition involves a loss of colonic structure and function and is considered a chronic process rather than an acute critical illness.

Risk factors and etiologies for GIDM

GIDM can result from both primary GI disease and secondary defects. Primary GI disease and gastric lesions can include inflammatory conditions (eg, inflammatory bowel disease[54]), GI ulceration,[55] infectious diseases (eg, parvoviral enteritis,[56,57] GI parasites, and bacterial infections), postoperative abdominal surgery, gastric neoplasia (eg, lymphoma, mast cell disease), and gastric dilatation and volvulus.[58] Secondary defects have been identified in veterinary patients and include acute stress,[59] inflammation of the viscera (eg, pancreatitis, peritonitis), electrolyte derangements, metabolic disturbances (eg, acidosis, hypoadrenocorticism, hepatic encephalopathy, uremia), drugs, diabetic gastroneuropathy,[60] splanchnic hypoperfusion, hypoxemia, obesity, the presence of SIRS or sepsis,[61] and neoplasia.[62,63]

A growing number of studies have been published evaluating the effects of experimental stress on GI function in animals and people.[59,64] Selective inhibition of gastric motility induced by noise stress in the dog has been associated with the CNS release of corticotropin releasing factor. Traumatic brain injury (TBI) has also been associated with dysmotility.[65,66] A prospective study of mechanically ventilated TBI human patients found that a significant percentage of postponed enteral feeding was related to ileus, with an average delay of 9 days, until maximum nutritional support following neurotrauma or neurosurgery.[66] Electrolyte disturbances have been shown to slow intestinal motility and have been demonstrated for hypokalemia,[67] hypermagnesemia,[68] and hyper- or hypocalcemia[69] in both dogs and human patients.

Many medications used to treat critically ill patients, including opioids and vasopressors, contribute significantly to motility disturbances. Opioids and enkephalins (ie, endogenous opioids) have been associated with GI ileus and dysmotility. Opioid peptides in the GI tract localized to enteric neurons and endocrine cells[70] have been shown to inhibit GI transit by reducing Ach release and altering neuronal excitability.[71] Opioids can also increase smooth muscle activity, but they inhibit coordinated propulsive peristalsis, leading to disordered nonpropulsive contractile activity.[72] In many animal models, even a fraction of the analgesic dose for an opiate was enough to inhibit intestinal motility.[73] Vasopressor agents and other catecholamines are used frequently to maintain hemodynamic stability of critically ill human patients in the intensive care unit (ICU). In vitro data have demonstrated a direct inhibitory effect of dopamine on small bowel motility in people.[74] In a human study investigating dopamine and motility via intestinal manometry, dopamine disrupted the fed motility pattern, decreased antral propulsive waves, and activated a duodenal phase III of MMCs.[75] Alpha 2-adrenoceptor agonists such as dexmedetomidine are utilized as additive analgesic drugs, sedatives to reduce analgesic and anesthetic requirements, and treatments for perioperative sympathoadrenal stability. However, these agents have been shown to have significant inhibitory effects on gastric, small intestinal, and colonic motility in veterinary and human patients.[76–78]

A high prevalence of delayed gastric emptying in patients with diabetes mellitus has also been demonstrated in several studies. In a sizeable series of human diabetic patients, delayed emptying of solid or liquid nutrition was observed in 40–50% of patients.[79] The pathophysiology in diabetics with GIDM may include diabetes-associated neuropathy, hypoglycemic and hyperglycemic effects on GI motor function, and insulin's effect on GI motility.[80] Autonomic neuropathies

are well characterized in diabetic patients, and vagal nerve dysfunction has been associated with delayed GI transit in both human and small animal veterinary patients. Hyperglycemia has been shown to reduce gastric antral contractions, suppress interdigestive phase III activity, and impair gall bladder emptying.[80] The role of tight glycemic control in critically ill human and small animal veterinary patients and its effect on GIDM is not completely understood and is frequently contested. There is some evidence that maintaining normoglycemia by intensive insulin therapy in critical illness minimizes feeding intolerance[81] and may improve immune function,[82] but the clinical benefit of this approach has been questioned.[83]

GIDM is a common manifestation of multiple system organ failure in the septic patient. Many mediators have been identified that lead to GI ileus, including tumor necrosis factor,[84] VIP,[85] and NO[86] in vivo. Postsurgical ileus can be seen as a result of a confluence of factors, including mechanical manipulation of the bowel, inflammation, pain, hormonal factors (eg, substance P, VIP, NO), concurrent medications (especially opioid medications), and electrolyte disturbances. Afferent neural signaling secondary to GI inflammation may affect increased sympathetic efferent activity via the splanchnic nerves, resulting in an overall shift toward decreased gut motility in postoperative ileus.[87]

Prevalence and incidence of GIDM

The prevalence of GIDM has not been concretely defined and varies widely according to the nature of the disease. Evidence of GIDM has been recently reported in 50–60% of critically ill human patients.[28,88] GIDM contributed significantly to prolonged ICU stays and increased morbidity and mortality. A study of human patients with TBI found that up to 80% of the patients had evidence of delayed gastric emptying and a delay of enteral nutrition (EN).[48] Another study found that EN was delayed in 251/400 patients (62.8%) of a population of critically ill human patients, and withdrawal of EN occurred in 15% of this population.[89] Patients with GI complications were also reported to have higher mortality rates compared to patients without documented complications. A human study utilizing a hydrogen breath test after lactulose demonstrated that 65% of patients in an ICU had a delayed GI transit time of >6 hours.[90] The prevalence of GIDM disorders in critically ill veterinary patients has not been reported.

Manifestations and Complications of GIDM

Consequences of GI hypomotility fall into 2 categories: (1) ingesta or food bolus stasis, and (2) disruption of normal absorptive function of the GI tract. Major consequences associated with GIDM include gastroesophageal reflux, esophagitis and aspiration, bacterial overgrowth, bloating or distension of the GI tract leading to increased IAP, fluid sequestration and hypovolemia, and delay of nutritional delivery (Table 1).

Table 1: Negative sequelae of gastrointestinal dysmotility

- Aspiration pneumonia
- Reflux esophagitis
- Bacterial overgrowth of the gut/bacterial translocation
- Abdominal distension/increased intra-abdominal pressure
- Fluid sequestration
  - Nutrient, water, and electrolyte loss
  - Hypovolemia
- Delayed delivery of nutrition

Gastroesophageal reflux and subsequent aspiration pneumonia are very common sequelae of GIDM in critically ill people, and small animal patients.[37,41,42,91–93] Gastroesophageal reflux occurs most commonly during and postanesthesia in small animal patients.[93,94] Prolonged anorexia and fasting may also contribute to reflux. One study suggests that fasting a dog for longer than 24 hours prior to an anesthetic event is more likely to cause reflux.[95] In a retrospective article evaluating aspiration pneumonia in dogs, the authors found that 23% of patients with GI dysfunction developed aspiration pneumonia.[96] Gastroesophageal reflux can also directly cause esophagitis, leading to complications with early EN and treatment.[97]

Abnormal GI motility has also been associated with bacterial colonization and overgrowth of the gut. GIDM can lead to an intolerance to enteral feeding, increased mucosal permeability for endoluminal mediators and bacteria, and the development of SIRS and sepsis.[38,98] One hypothesis, often referred to as "gut-derived sepsis," describes bacterial translocation from the gut, promotion of septicemia, and eventual multiorgan dysfunction.[99–101] Several medical reports have indicated that people's gut flora can also directly affect the ENS and motility in the gut.[102,103] In people with SIRS, investigators found that GIDM was associated with altered gut flora as well as with higher septic mortality.[39] GI hypomotility in veterinary patients has been associated with abdominal distension and may result in

increased IAP, abdominal compartment syndrome, and the development of systemic consequences, especially organ function impairment.[104] In critically ill people with ileus, increased luminal contents (ie, GI distension) and bacterial overgrowth have been directly correlated with increased abdominal pressure and can perpetuate compartment syndrome.[105,106]

Ileus has been associated with fluid sequestration and subsequent hypovolemia in critically ill human and small animal patients. Intestinal dilation, with a concomitant rise of intraluminal pressure and IAP, jeopardizes intestinal perfusion, compromises microcirculation, and ultimately results in fluid sequestration into the intestinal wall and lumen.[107] In a functional ileus, intestinal distension is exacerbated by inflammation of the intestinal wall, promoting fluid loss into the luminal space. This fluid sequestration, or "third spacing," can result in hypovolemia and microcirculatory impairment. Osmotic diarrhea due to the presence of unabsorbed nutrients into the colon can be severe enough to exacerbate hypovolemia, and can potentially aggravate malabsorption.[108] Fluid and circulatory management is imperative to prevent these developments from occurring, which presents an essential component in the therapy of patients with ileus.

GI motility dysfunction has a profound impact on nutrition delivery as well as on absorption in critically ill patients. A highly recommended practice, early EN has been associated with decreased morbidity and mortality in critically ill human and small animal patients.[109] Clinical signs of GIDM were evaluated in recent retrospective studies of critically ill dogs undergoing nasoenteric feeding.[110,111] The prevalence of vomiting and regurgitation was found to be 11%[110] of patients in one study and 24–26%[111] in another study population. In a multicenter study evaluating enteral feeding in 200 critically ill human patients, about 25% of them had inadequate nutritional delivery as a result of GIDM and dysfunction.[3] Patterns of motor dysfunction can cause either rapid small intestinal transit, resulting in poor absorption of nutrients and perpetuating diarrhea, or reduced absorption as a result of impaired mucosal function. Impaired absorption of oral medications may also contribute significantly toward failure of therapy in critically ill small animal patients.[112]

Diagnosis

Diagnosis of GIDM in small animals is mainly inferred when there is clinical evidence of abnormal motility. Clinical signs such as anorexia, abdominal pain, abdominal distension, nausea, vomiting, and increased volume of gastric residual volumes (GRVs) can provide a subjective assessment of GI motility. Definitive measurements of GI motility in small animal veterinary patients may be difficult to obtain in the ICU environment because of the expense associated with the necessary specialized equipment. A more objective assessment of GI motility may, however, help guide treatment and prophylactic therapies. A number of veterinary diagnostic modalities have been utilized to investigate GI function in the small animal ICU.[113]

Radiography

Contrast radiography can be used to assess GI motility disturbances in critically ill dogs and cats. The GI passage of radiopaque solids and liquids has been monitored using radiographic and fluoroscopic methods, providing a qualitative interpretation of the rate of GI transit. Radiopaque test meals administered to both dogs and cats included liquid barium,[113] barium mixed with food,[114–116] and radiopaque indigestible materials (eg, barium-impregnated polyethylene spheres).[117,118] The availability of basic radiographic equipment makes this method a useful tool for investigating obvious gastric emptying abnormalities, but it has limited utility in the evaluation of subtle GI motility disorders in critical illness.[119] Additional limitations include administration of a meal to an anorectic patient, and risk of regurgitating or vomiting.

Ultrasonography

Ultrasound is now available in many veterinary practices and may be useful as a noninvasive tool for a qualitative and semiquantitative assessment of delayed gastric emptying and ileus in critically ill small animal patients. Gastric emptying measurements and small intestinal peristalsis using ultrasound have been investigated in dogs[120–123] and have been validated and applied in human medicine.[124] Ultrasound has notable advantages over other tools: GI motility may be evaluated with limited restraint, and the technology is widely available. The main disadvantages of ultrasonography are its inherent subjectivity, the lack of reference ranges in healthy and diseased animals, and a lack of consensus on reference ranges in dogs and cats. McLellan et al[122] recently compared a ^{13}C octanoic acid (^{13}C-octanoate) breath test and a gastric emptying ultrasound in healthy dogs and found a moderate, but statistically significant, association between the rate of gastric emptying of a semisolid test meal assessed by both techniques.

GRVs

The measurement of GRVs can quantify and evaluate gastric tolerance of EN and subjectively assess the degree of dysmotility. Calculated EN and fluid retention

can be used as an indirect methodology for evaluating delayed gastric emptying. GRV-driven nutritional support algorithms are utilized to guide nutritional prescription strategies in many human ICUs[125–127]; however, the association between pulmonary aspiration and GRV is still inconsistent. In a recent veterinary study, researchers compared intermittent and continuous EN strategies in critically ill dogs and also measured GRV.[111] They found no direct association between GRV, the occurrence of vomiting or regurgitation, or incidences of aspiration. Therefore, the use of GRV to guide treatment strategies should be approached with caution until additional studies have been conducted.

Specialized testing

More specialized testing modalities have been examined in human and animal models of GIDM, including radioscintigraphy,[128] ^{13}C breath tests,[129] lactulose breath tests,[130] manometry,[131,132] tracer studies,[133] and MRI.[134] Imaging of the passage of a radiolabeled test meal by use of gamma camera (ie, radioscintigraphy) is the research standard for assessing gastric emptying[128]; however, it is not readily available in clinical practice. The ^{13}C breath tests (eg, ^{13}C-octanoate and ^{13}C-glycine) are a noninvasive method for assessment utilized widely in human research medicine, and the effectiveness of the ^{13}C-acetate breath test has recently been validated in dogs.[129]

Small intestinal transit times have been evaluated with a lactulose breath hydrogen test. Researchers evaluated orocaecal transit time in six healthy dogs with a hydrogen breath test using lactulose and the sulphasalazine/sulphapyridine method, where both techniques were validated.[130] Multiple-channel manometry is the measurement of intraluminal pressure by a fluoroscopically guided multilumen catheter at various locations in the GI tract; ambulatory manometry has been introduced and can be performed in the awake people and has been utilized recently in nonsedated dogs.[132,135] The applications of many of these modalities are limited and not widely available to practicing veterinary clinicians.

Therapeutic Strategies

The mainstays of treatment for GIDM include identification and treatment of the predisposing illness, early nutritional intervention, judicious fluid therapy, early ambulation, correction of metabolic derangements, maintenance of normothermia, multimodal pain management, and pharmacological intervention (Table 2). Other primary causes of GI motility disorders should also be excluded prior to the diagnosis of GIDM secondary to critical illness.

Early EN

Disruption of normal GI motor function can lead to intolerance of enteral feeding, increased mucosal permeability for bacteria and circulating mediators, and the development of SIRS.[48] Early EN has improved the treatment of critically ill small animal veterinary patients, and it remains an important treatment strategy.[57,136–138] Proposed mechanisms supporting early EN include improving blood flow to the gut, protecting the GI mucosa, reducing the risk of translocation of intestinal bacteria, stimulating motility, and promoting secretion of various gut hormones and growth factors.[1,139–141] In a recent study, researchers demonstrated that early EN was associated with shorter hospitalization time in a group of dogs with naturally occurring septic peritonitis.[138] In a study of critically ill and artificially ventilated people, starting EN within 48 hours of mechanical ventilation was associated with up to a 20% decrease in mortality in the ICU and a 25% decrease in hospital mortality.[142]

Enteral formulations and modalities have been investigated in the treatment of GIDM. Meal viscosity can influence gastric emptying and has been shown to be affected by water intake, meal size, and food type (moist vs. dry food) in both dogs and cats. [29,143] Definitive enteral formulation recommendations for GIDM have not been investigated in veterinary medicine. A number of human studies have been performed comparing gastric with small intestinal feeding in patients with GIDM.[144–146] Interestingly, the efficacy of nasojejunal feeding and postpyloric feeding protocols have been called into question as compared to gastric feeding due to a lack of benefit found in a recent study.[108]

Fluid therapy

Fluid resuscitation strategies have been debated recently in critical care medicine with regard to optimal approaches for preserving GI motility. Inadequate fluid resuscitation has been associated with decreased gut perfusion. In elective human cardiac surgery patients, perioperative plasma volume expansion with a colloid reduced the incidence of gut mucosal hypoperfusion and decreased hospitalization time.[147] Additionally, aggressive fluid resuscitation with subsequent intestinal edema and its detrimental effect on GI motility has also been well recognized.[148,149] Recently, researchers have shown that gut edema induced in an experimental rat model resulted in depression of intestinal transit, an increased intestinal permeability to macromolecules, and a decreased tissue resistance over time.[150] The same research group also demonstrated that human patients receiving resuscitation fluids resulting in GI tract edema had decreased stiffness and residual stress of the intestine, offering a mechanical explanation for gut

Table 2: Strategies for prevention and treatment of gastrointestinal dysmotility of critical illness in small animals

Category	Specific action	Physiologic effect/proposed benefit
Pharmacologic intervention	Prokinetic drugs Opioid antagonists	Improve motility
Metabolic	Maintain electrolyte homeostasis Maintain normal acid-base balance Normothermia	Improve metabolic derangements and decrease inhibitory effect on motility
Early mobilization	Ambulate early	Stimulate bowel activity
Pain management	Provide adequate analgesia Minimize use of opiates – consider regional analgesia and multimodal pain management	Decrease inhibitory effect of opioids on motility
Fluid resuscitation	Maintain adequate intravascular volume Avoid excessive hydration/volume overload	Adequate GI perfusion Minimize bowel edema
Early enteral nutrition	Early postoperative feedings Selective use of feeding tubes/gastric decompression	Improving blood flow to the gut Stimulate GI motility Secretion of various hormones and growth factors

GI, gastrointestinal.

edema-induced ileus.[151] The cellular mechanisms by which gut edema affects intestinal transit are not completely understood, but the presence of nuclear factor kappa B[152] and increased expression of inducible NO synthase and subsequent NO production have been suggested.[153] Nuclear factor kappa B is hypothesized to trigger a gene regulation program leading to decreased myosin light-chain phosphorylation and, thus, decreased intestinal contractile activity.[152] Increased NO upregulates smooth muscle cyclic guanosine monophosphate, effectively deterring smooth muscle contractility by impeding myosin light chain phosphorylation and actin/myosin cross-linking.[150]

Limited volume fluid resuscitation strategies to avoid interstitial and intestinal edema have been evaluated in several recent human studies.[151,154,155] Judicious use of adjunctive fluid products, including hypertonic saline and colloids, has been emphasized. A small percentage of crystalloid fluids have been shown to remain within the intravascular space and volumes may be even less in states of increased endothelial permeability.[156] Hypertonic saline has been recommended and evaluated as it has been shown to alter hydraulic conductivity, decrease intestinal edema, and improve overall GI transit.[149,157] While there is a shift toward limited fluid resuscitation strategies to avoid intestinal edema, definitive recommendations have not been made and adequate perfusion of the patient should be prioritized. Striking a balance, in terms of both fluid composition and volume, is likely to reduce the morbidity associated with interstitial and intestinal edema. This balance may be best achieved using individualized and goal-directed approaches to fluid therapy, adjunctive use of colloids and hypertonic saline, and frequent monitoring to prevent edema from occurring.

Early ambulation

It has traditionally been thought that early ambulation exerts a prokinetic effect on GI motility, and as a result, early ambulation has become a central component of the management of ileus.[158,159] However, few studies and little evidence support this treatment recommendation. A single study has been performed looking at the effects of early ambulation on stomach, small bowel, and colonic motility in humans.[160] In this study, no correlation was found between early ambulation and the resolution of postoperative ileus. Despite this lack of evidence, ambulation still remains a frequent recommendation in the human literature, due in part to the correlation between early ambulation and a decreased risk of developing postoperative respiratory and thrombotic complications. In the small animal veterinary literature, no studies evaluate the relationship between early ambulation and ileus.

Multimodal pain management

Pain management should always be carefully considered in the critically ill patient. Inadequate pain management has been shown to increase morbidity and worsen patient outcomes.[161] In critically ill veterinary patients, opioids often are the safest and offer the

most effective pain relief. However, the relationship between pure mu opioid receptor agonists and ileus has been well documented. Various opioids have different effects depending on concentration and strength, but opioid derivatives will affect GI motility to some degree in more than 50% of opioid-treated human patients, according to one study.[162] Opioid selection should take into consideration its effect on motility and other patient factors. Animal and human studies have suggested that there is variability among opioids in the plasma concentrations required to cause ileus and analgesia.[163–165] Some opioids such as morphine require a much smaller concentration to cause ileus, whereas similar concentrations are required for fentanyl to exert both analgesic and altered motility.[163,166] Multimodal analgesic plans should also be considered in all critically ill small animal veterinary patients in order to avoid GIDM. Continuous post-operative epidural analgesia is one viable option, as several human studies have shown that local anesthetics are the most effective means of preventing postoperative ileus.[167,168] Nonsteroidal anti-inflammatories may also be effective in achieving multimodal analgesia with minimal effect on gut motility.[169] Unfortunately, nonsteroidal anti-inflammatory agents may be contraindicated in many critically ill small animal patients and should be used judiciously.

Other therapeutic options

Many other alternative therapeutic strategies have been evaluated in animal and human studies for the treatment of GIDM including other pharmacologic agents, Chinese herbal medications (*Saussurea lappa*,[170] rhubarb[171]), and acupuncture,[172–174] although results have been variable. Vasopressin has been reported to have motility modulating effects on the GI tract in people and animals, although studies are unclear and conflicting about its overall effect on motility.[175–177] These motility modulating effects could have resulted from vasopressin-mediated stimulation of sodium chloride and water absorption, as well as inhibition of chloride secretion in mouse, rat, and human colon.[178] Vasopressin also may act as a neuromodulator of enteric cholinergic neurons inducing excitatory effects on the contractility via V1a receptors.

Specific Pharmacological Interventions

Prokinetic drug therapy is a noninvasive and relatively inexpensive means of improving GI motility. Understanding the receptors involved and the localization of GIDM is necessary for the success of a prokinetic medication protocol. A variety of prokinetic agents have been used to treat GIDM in small animal veterinary medicine. These drug mechanisms of action and dosages are summarized in Table 3. Many findings regarding motility medications in the small animal veterinary literature are from in vivo and in vitro studies conducted in small mammals and dogs as models for people.

Dopaminergic receptor (D_2) antagonists

Within the myenteric plexus, dopaminergic receptor activation results in decreased Ach release and decreased smooth muscle activity. Dopaminergic antagonists, therefore, indirectly increase Ach release from postganglionic cholinergic neurons and promote intestinal smooth-muscle contraction and peristalsis.[5] However, the importance and role of dopaminergic innervation in the gut is not completely understood, and the source (neuronal vs. non-neuronal) of enteric dopamine remains controversial.[179,180] Nevertheless, dopaminergic antagonist properties of various promotility agents are still referenced. Medications utilized commonly in veterinary medicine that have dopaminergic antagonistic activity include domperidone, (D_2 receptor), and metoclopramide (D_2 receptor).

Domperidone

Domperidone acts as a peripheral D_2 antagonist and has α_2- and β_2-adrenergic receptor antagonistic effects.[53,181] The prokinetic effects of dopaminergic antagonists may not be entirely explained by inhibition of dopaminergic neurons, likely owing more to the adrenergic antagonistic effects.[53] Domperidone seems to be less efficacious than metoclopramide as a gastric prokinetic[182] and may actually decrease the frequency of corporeal, pyloric, and duodenal contractions and deteriorate antropyloroduodenal coordination in the dog.[183] It also has minimal phasic effects on the LES and therefore has limited use for gastroesophageal reflux, and it has no documented small intestinal effects on transit. The major clinical utility of domperidone lies in its potent antiemetic effects, as it is 12–25 times stronger compared to metoclopramide and has been shown in dogs to attenuate apomorphine-induced vomiting.[184] The dose range of domperidone in dogs and cats is 0.05–0.1 mg/kg per os once or twice daily. The use of domperidone in veterinary species is not approved in the United States, and domperidone's lack of efficacy with regards to promotility compared to other available prokinetic agents limits its use in practice.

Serotonin receptor (5-HT) agonists, antagonists

Serotonin (5-HT) is extensively studied as a neurotransmitter in the CNS, but it also plays an important role in modulating GI motility. 5-HT released from enterochromaffin cells of the GI mucosa activates neural pathways

Table 3: Doses and properties of common prokinetic agents used in veterinary medicine

Drug name	Prokinetic mechanism of action	Dose
Metoclopramide	Dopaminergic (D_2) antagonist Serotonergic agonist (5HT4)	0.2–0.5 mg/kg PO, IV, SQ q8h CRI: 1–2 mg/kg/d IV
Domperidone Cisapride	Dopaminergic (D_2) antagonist Serotonergic agonist ($5HT_4$) Serotonergic antagonist ($5HT_{1,3}$)	0.05–0.1 mg/kg PO q12h 0.2–1.0 mg/kg PO q8h in dogs 2.5 mg/cat, q8h for cats $<$5 kg 5.0 mg/cat q8h for cats $>$5 kg
Erythromycin	Motilin agonist Serotonergic antagonist ($5HT_3$)	0.5–1.0 mg/kg, IV, PO q8h–q12h
Ranitidine	Acetylcholinesterase inhibitors H_2 – histaminergic antagonist	1.0–2.0 mg/kg PO q8h–q12h
Nizatidine	Acetylcholinesterase inhibitors H_2 – histaminergic antagonist	2.5–5.0 mg/kg PO q24h

PO, per os; IV, intravenous; SQ, subcutaneous; CRI, constant rate infusion.

associated with secretion, peristalsis and motility, and sensation.[185] The role of 5-HT in the gut is complex and involves multiple receptor subtypes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7) present in the GI tract.[186] Motility of the gut is mainly regulated by receptor 5-HT_4. Presynaptic 5-HT_4 stimulates Ach release from postganglionic cholinergic neurons, resulting in smooth-muscle contraction.[53,187] 5-HT_4 receptor agonist-targeted medications are thought to promote contraction of the smooth muscle cell, thereby improving GI contractility. Many of these therapeutic agents also involve other 5-HT receptors (eg, 5-HT_1, 5-HT_3) in motility enhancement and antiemetic effects. Antagonism of the 5-HT_3 receptor by medications such as ondansetron and dolasetron can be used to treat nausea secondary to delayed gastric emptying but have failed to demonstrate a direct effect on motility. Medications utilized commonly in veterinary medicine that have serotonergic activity include cisapride ($5HT_4$ agonist, $5HT_1$, and $5HT_3$ antagonist) and metoclopramide ($5HT_4$ agonist, $5HT_3$ antagonist).

Cisapride

Cisapride is a prokinetic agent whose mechanism is thought to involve enhancement of the physiological release of Ach from postganglionic nerve endings of the myenteric plexus in GI smooth muscle.[188] Cisapride acts as a prokinetic indirectly by functioning as a parasympathomimetic and increasing Ach release achieved by increasing 5-HT. Further, it has a direct prokinetic effect via 5-HT_4 agonism of the ENS.[188,189] Cisapride also has antagonistic effects at 5-HT_1 and 5-HT_3 receptors[190] of the enteric cholinergic neurons and direct agonistic effects (5-$HT_{2\alpha}$) on colonic smooth muscle.[53]

Cisapride stimulates distal esophageal peristalsis in species with smooth muscle (such as cats and people). The notable exception is in dogs, which does not have any smooth muscle in the esophagus. Cisapride stimulates gastric emptying, increases gastroesophageal sphincter pressure, and enhances antropyloroduodenal coordination. It is has been shown to be more potent than metoclopramide in combating delayed gastric emptying in small animal patients.[191,192] Cisapride is one of the few prokinetics that affects small intestinal motility by stimulating jejunal spike burst migration, jejunal propulsive motility, and antropyloroduodenal coordination.[193,194] Cisapride also stimulates colonic motility and can be justified as a treatment of idiopathic constipation and colonic pseudo-obstruction.[195–197]

The dose of cisapride to enhance gastric emptying in dogs with normal function is 0.05–0.2 mg/kg per os; however, in patients with delayed gastric emptying (specifically, secondary to alpha-$_2$ adrenergic agonists, dopamine, or antral tachygastria) higher doses of 0.5–1.0 mg/kg per os may be needed.[53] Side effects of cisapride in people include QT interval prolongation and slowing of cardiac repolarization via a blockade of the rapid component of the delayed rectifier potassium channel, and these side effects led to the drug's withdrawal from the human market. [198] This complication has not been documented in small animal veterinary medicine, but has been shown in an induced canine model using doses from 0.6 to 6 mg/kg.[199] Other side effects of cisapride include increased defecation, head pain, abdominal pain, cramping, and flatulence. An oral formulation is readily available at compounding pharmacies, and a parenteral formulation is available at a limited number of pharmacies across the United States.

Metoclopramide

Metoclopramide (2-methoxy-5-chloroprocainamide) acts as a dopaminergic antagonist (mainly affecting the D_2 receptor subtypes), serotonin $5HT_4$ agonist, and $5HT_3$ receptor antagonist.[5,190] Through its dopaminergic and $5HT_3$ antagonism, metoclopramide acts as an antiemetic by preventing stimulation of the chemoreceptor trigger zone. Metoclopramide's effects on GI motility and the improved coordination of the gastropyloric small intestinal motor function are due mainly to its $5HT_4$ agonism, and dopaminergic antagonism,[5,53] although the role of dopamine and motility in the GI tract is unclear. Metoclopramide should be considered a less effective promotility drug and may be more important as an antiemetic.[5]

Metoclopramide has been shown to potentiate lower esophageal tone, decrease fundic receptive relaxation, and increase gastric emptying in veterinary species.[200] Metoclopramide has no documented effects in the distal small intestine or in the colon, and it should only be used for upper GI motility disorders.[53] Metoclopramide reestablishes antropyloroduodenal coordination in states of delayed gastric emptying.[44,53,183] Coordination of the upper GI tract results in accelerated gastric emptying and reduced esophageal reflux.[183,201] A recent study addressed the role of metoclopramide in increasing gastroesophageal sphincter tone in a group of anesthetized healthy dogs.[202] The results of the study indicated that 25/52 dogs had at least one episode of gastroesophageal reflux while under anesthesia, and using a high-dose regimen (1 mg/kg intravenous bolus followed by 1 mg/kg/h IV) of preanesthetic metoclopramide significantly decreased the number of reflux events. The effects of anticholinergics (eg, atropine, glycopyrrolate) and prokinetic agents (eg, metoclopramide, cisapride) on antral motility were evaluated using passive telemetry in Beagles and Labrador Retrievers.[191] This study found that there was distinct breed and dose differences noted where lower doses of metoclopramide (0.3 mg/kg per os) and cisapride (0.2 mg/kg per os) resulted in improved antral motility in the Beagles, and only the higher doses (metoclopramide 0.6 mg/kg per os, cisapride 0.5 mg/kg per os) of both prokinetic agents showed a significant difference in the Labrador Retriever group.[191] These results suggest that dosing of metoclopramide may need to be higher than current recommendations and breed difference should be noted.

Metoclopramide has a short half-life (3–4 h) and is usually administered up to 4× daily by subcutaneous injection, orally, or as a constant rate infusion (CRI). The prokinetic dose of metoclopramide in dogs and cats is 1.0–2.0 mg/kg/d IV as a CRI or 0.2–0.4 mg/kg 3× daily subcutaneously. Investigators have recently attempted to prepare a semisolid polyorthoester as an injectable bioerodible polymer for the controlled release of metoclopramide with some success.[203] A controlled release formulation of metoclopramide could be beneficial in small animal veterinary patients with evidence of prolonged impaired gastric emptying and intolerance to oral administration of medications. Metoclopramide may also enhance the bioavailability of cyclosporine, although it does not have significant inhibition of CYP3A enzymes.[204] It has also been hypothesized that metoclopramide increases circulating prolactin, inducing an analgesic effect, although this has only been evaluated in experimental models.[205]

The most common side effects of metoclopramide include adverse effects collectively called "extrapyramidal signs" with a reported incidence of 0.2%.[206] In high-risk human patients, the risk of these side effect can increase up to as high as 25%.[206] Dopamine antagonism in the striatum causes extrapyramidal signs including involuntary muscle spasms, motor restlessness, and inappropriate aggression. These signs have been reported to be reversed by restoring an appropriate dopamine:Ach balance and symptomatic treatment with various medications including antihistamines, benzodiazepines, beta-adrenergic antagonists (eg, propranolol), or dopamine agonists (eg, amantadine).[207]

Novel serotonin agonists

Novel serotonin agonists that are currently under investigation in human and animal studies include velusetrag (TD-5108),[208] tegaserod,[209] mosapride,[210,211] and prucalopride.[212–214] Mosapride is a novel 5-HT_4 receptor agonist that enhances GI motility. It is used as a prokinetic in people and has recently been evaluated for use in dogs.[210,215] Tegaserod, a potent partial 5-HT_4 agonist and a weak 5-HT_{1D} receptor agonist, has been shown to increase antral, duodenal, jejunal, and colonic motility in conscious dogs.[216,217] Studies by Nguyen et al[218] using varying doses of tegaserod in dogs showed acceleration in colonic transit, although the effects on upper GI transit were more variable.[209,217] Tegaserod has been investigated for postoperative ileus in horses[219,220]; however, clinical trials of tegaserod in small animal veterinary medicine are lacking.

Motilin and ghrelin receptor agonists

Motilin is a peptide synthesized by endocrine cells of small intestinal mucosa. Ghrelin is a similarly composed peptide produced by the parietal cells of the gastric mucosa as an endogenous ligand for growth hormone. Motilin and ghrelin precursors share roughly 50% similarity in their amino-acid sequences and are now grouped into a new motilin-ghrelin peptide family.[221] Motilin regulates the interdigestive MMC. Cycling

plasma levels of motilin increase every 90–120 minutes during the interdigestive period, and motilin release disappears after ingestion of a meal.[222,223] These cyclical peaks of plasma motilin correlate with strong peristaltic contractions (phase III of MMC) initiated from the stomach and migrate aborally to the small intestine. Motilin receptors are located on cholinergic nerves, and they have been isolated from the smooth muscle of the GI tract in several species.[224,225] Ghrelin, a peptide which binds to the ghrelin receptor, is also released by the GI tract during fasting. The ghrelin receptor is found primarily in the endocrine cells of the gastric mucosa, and it increases gastric emptying and MMC (phase III-like) activity.[226] Medications utilized commonly in veterinary medicine that are motilin and ghrelin agonists include erythromycin (motilin agonist) and azithromycin (motilin agonist).

Erythromycin/azithromycin

Erythromycin is a macrolide antimicrobial that increases GI motility by acting on motilin receptors in the smooth muscle cells of the GI tract.[227] Erythromycin mimics the effects of motilin on the upper GI tract and stimulates motility. There are species differences in its mechanism of action. In dogs, this effect is mediated through 5-HT_3 cholinergic pathways, whereas in cats the effect occurs via direct stimulation of smooth muscle motilin receptors.[53] In many species, erythromycin has been shown to lower LES tone, increase antral contractions and gastric emptying, and decrease small intestinal transit time.[228] Studies in critically ill human patients demonstrate improved gastric motility and decreased GRVs in patients treated with low-dose erythromycin.[229–231] In a population of mechanically ventilated human patients, erythromycin decreased the time to tolerated early EN.[232] In a recent study of critically ill human patients, erythromycin was found to be superior to metoclopramide in decreasing GRVs in the short-term treatment of feed intolerance, and it showed greater efficacy in nasogastric feeding for a longer period of time.[229] In this same study, combination therapy with both treatments was shown to be highly effective in patients that had failed monotherapy. Veterinary patients have also shown promising responses to erythromycin: a study of denervated dogs demonstrated a responsive burst of contractions (similar to the MMC) in the antrum of the stomach and duodenum.[233,234] The dose of erythromycin in veterinary patients as a prokinetic is 0.5–1.0 mg/kg per os or IV 2–3× daily. High doses of erythromycin (10–30 mg/kg) have actually been shown to stimulate retrograde peristalsis, and that the lower microbially ineffective dose (1–5 mg/kg) stimulates MMCs and antegrade peristalsis.[5,235,236] Side effects of erythromycin are rare and it is generally well tolerated by animals. Most side effects occur with high doses of erythromycin and include Q-T prolongation,[237] nausea, and inappetance.

Azithromycin is another macrolide antibiotic that is currently being studied for its prokinetic properties. In manometric human and animal studies comparing azithromycin and erythromycin as prokinetic agents, azithromycin was found to be at least as potent as erythromycin in stimulating antral contractility.[238,239] Azithromycin may, therefore, provide an alternative to erythromycin for gastroprokinetic applications. Concerns regarding azithromycin and erythromycin use in human medicine include the potential rise in antibiotic resistance.[240] Nonantibiotic motilin and ghrelin agonists would eliminate such a concern and are currently being investigated and developed. Novel ghrelin/motilin analogues/receptor agonists investigated in dog experimental models for the treatment of delayed gastric emptying and ileus include MTL-RP/ghrelin,[241] CGRP 8-37,[241] and GS-611.[242]

Histamine receptor antagonists

The biological effects of histamine on GI motility are complex and involve both neurally regulated and direct effects on smooth muscle contractility. These effects are mediated through different histamine receptors including H_1, H_2, and H_3.[243–245] Species variability exists with location, tissue type, and prevalence of receptor subtypes.[246] All histamine receptors are present in the GI tract, but their predominant action and influence vary. Histamine H_1 receptor activation causes contraction similar to that of muscarinic receptor activation by increasing calcium availability.[247] Histamine H_2 receptors can mediate neurogenic contractions by facilitating both cholinergic and noncholinergic excitatory transmission.[246,248] H_2 receptor antagonists are used widely for the treatment of gastric acid related disease in dogs and cats, while agents ranitidine and nazitidine are utilized for their prokinetic effect via acetylcholinesterase inhibition. The novel third histamine receptor type, histamine H_3 receptor, has been recently identified and localized throughout the GI tract,[243] however experimentally it has been shown to play a very minor role in regulation of GI motility. Histamine H_3 receptor subtype has only been isolated in the human intestinal tract and has not been evaluated as a potential therapeutic target in small animal veterinary species.[245,247]

Ranitidine/nazitidine

Ranitidine and nizatidine are histaminergic receptor (H_2) antagonists that are used to suppress gastric acid secretion. These medications have also been shown to promote acetylcholinesterase inhibition within the ENS

and to stimulate GI motility in dogs and cats.[249] By decreasing acetylcholinesterase at the neuromuscular junction, these drugs prolong and enhance the effects of Ach smooth muscle contraction. Both agents function primarily on smooth muscle and affect delayed gastric emptying, ileus, and colonic motility.[5] These medications have questionable efficacy in critically ill patients compared to other prokinetic agents, and other medications should be considered. The prokinetic effects of ranitidine and nizatidine are functional at antacid doses (ranitidine 2 mg/kg 2× per day, orally/IV; nizatidine 2.5–5.0 mg/kg/d orally).

Opioid receptor antagonists

Opioid peptides and receptors have been identified and isolated throughout the GI tract, indicating that endogenous opiates may modulate GI motor and secretory functions. GIDM and ileus are the most common and serious adverse effects of opioid analgesics.[72,250] Hypomotility results from this decreased neurotransmission and inhibition of neuronal firing at both the level of the CNS and of the enteric neurons in the GI tract.[251,252]

Activation of opioid receptors is common after surgery and critical illness, not only because of the release of endogenous opioids but also because opioids remain the most common treatment for postoperative pain. Morphine and opioid analgesics inhibit the release of Ach, thereby increasing colonic muscle tone and reducing propulsive activity in the GI tract. The GI consequences of opioids can be moderated by the oral administration of antagonists such as naloxone[253,254] and alvimopan.[255] Naloxone has been shown to increase gastric emptying in people.[256] Enteral administration has resulted in blocking opioid action at the intestinal receptor level, but naloxone has limited bioavailability and systemic antagonistic effects due to hepatic first-pass metabolism. In recent years, quartenary opioid (mu) antagonists alvimopan and methylnaltrexone have been investigated. These compounds antagonize the inhibitor effects of opioids on gut motility but do not cross the blood-brain barrier and therefore do not antagonize the analgesic effects of opiates. Alvimopan is a potent orally active mu opioid receptor antagonist (highly selective) that has been approved by the US Food and Drug Administration to treat postoperative ileus in people.[257,258] Its use is limited to veterinary experimental studies mainly due to concerns regarding the cost-benefit ratio of this drug, given that alvimopan costs nearly US$1,000/treatment cycle in human medicine. Another opioid antagonist, methylnaltrexone, has restricted ability to cross the blood-brain barrier in people because of its polarity and low lipid solubility.[259] Methylnaltrexone demonstrated efficacy in 2 double-blind trials and is used in opioid-induced constipation.[73] Other novel opiate antagonists, including NKTR-118,[260] TD-1211,[261] ADL-7445, and ADL-5945, are currently being investigated and have shown significant promise as a new approach to GIDM.[262–264]

Novel future pharmacologic targets for GIDM

Due to the complexity of GI motility disorders, many novel therapies targeting different receptors are currently under investigation in both human and animal studies. These receptors include type-2 chloride channel activators,[265,266] CCK receptor antagonists,[267–269] guanylate cyclase 2C agonists,[270,271] and ileal bile acid transporter antagonists.[272,273] Lubiprostone, a type-2 chloride channel (CIC-2) activator, activates chloride receptors located on gut epithelial cells and drives chloride ions into the gut lumen, inducing intestinal fluid secretion and increasing intestinal motility.[265] CCK-1 (CCK-1) receptor antagonists, including loxiglumide and dexloxiglumide, have been shown in animal and human studies to have an effect on the colonic muscle and improve colonic transit time.[45,267,268] Guanylate cyclase 2C agonists, including linaclotide, bind to guanylate cyclase C receptors in the gut epithelium resulting in a large increase in secretion of chloride, bicarbonate anions, and fluid secretion into the gut thereby enhancing motility.[271] Ileal bile acid transporter inhibitors act locally in the gut to inhibit the reuptake of bile acids and, in turn, increase motility. A3309, an ileal bile acid transporter, has been shown to decrease constipation and ileus in a dog experimental model.[272]

Prognosis

An increase in morbidity and mortality has been seen in critically ill people with evidence of GIDM compared to patients without.[37,41,42,91–93] There are currently no standard guidelines regarding initiation of prophylactic measures, preference of pharmacological intervention and treatment modality, or how to definitely identify GIDM in critically ill dogs and cats. Extrapolation from human literature, however, emphasizes the importance of early identification and intervention in our small animal veterinary patients. The prognosis for GIDM depends on the underlying disease processes and severity of illness. Failure of treatment due to GIDM can be from poor drug penetration, impaired drug absorption, ongoing comorbid diseases, and failure of adequate nutritional delivery.

Summary

GIDM is a common sequelae in critically ill human and small animal veterinary patients where adverse effects associated with dysmotility can have a significant impact on patient morbidity and mortality, as well as on

hospitalization time. Although GIDM has not yet been well characterized in small animal veterinary patients, animals share the same predisposing factors as human patients. There is an evolving understanding of GI pathophysiology in critical illness that includes dysmotility causing delayed gastric emptying, ileus, and impaired intestinal nutrient absorption. Practical early diagnosis of GIDM consists mainly of identifying clinical signs and the presence of excessive GRVs if available. Treatment of GIDM is multimodal and should be implemented by taking individual patient factors into account. Early EN appears to stimulate the return of normal bowel function and exerts a prokinetic effect. Adequate hydration and electrolyte balance should be maintained, but gut edema should be avoided at all times when implementing a fluid resuscitation plan. Alternative modes of analgesia, including local anesthesia, should be utilized, especially when attempting to decrease opioid use in postoperative patients. Prokinetic therapy in patients with GIDM of critical illness is recommended; however, due to the lack of evidence for a single prokinetic, a multimodal approach should be utilized. Human and animal studies have suggested that early judicious nutritional support in addition to a combination of prokinetic drugs based on GI localization of clinical signs is superior to delayed EN and monotherapy with prokinetic agents. Further studies are necessary in order to investigate the incidence of GIDM in small animal veterinary patients as well as the effects of GIDM on morbidity, mortality, and duration of hospitalization.

References

1. Braga M, Gianotti L, Gentilini O, et al. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. Crit Care Med 2001; 29(2):242–248.
2. Hansen MB. Neurohumoral control of gastrointestinal motility. Physiol Res 2003; 52(1):1–30.
3. Adam S, Baston S. A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. Intensive Care Med 1997; 3(23):261–266.
4. Fruhwald S, Holzer P, Metzler H. Intestinal motility disturbances in intensive care patients pathogenesis and clinical impact. Intensive Care Med 2007; 33(1):36–44.
5. Washabau RJ. Gastrointestinal motility disorders and gastrointestinal prokinetic therapy. Vet Clin North Am Small Anim Pract 2003; 33(5):1007–1028.
6. Boillat C, Gaschen F, Gaschen L. Variability associated with repeated measurements of gastrointestinal tract motility in dogs obtained by use of a wireless motility capsule system and scintigraphy. Am J Vet Res 2010; 71(8):903–907.
7. Holzer P, Schicho R, Holzer-Petsche U, et al. The gut as a neurological organ. Wien Klin Wochenschr 2001; 113(17/18):647–660.
8. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. Gut 2013; 62(8):1214–1222.
9. Schmidt PT, Holst JJ. Tachykinins in regulation of gastric motility and secretion. Cell Mol Life Sci 2000; 57(4):579–588.
10. Maggi CA, Catalioto RM, Criscuoli M, et al. Tachykinin receptors and intestinal motility. Can J Physiol Pharmacol 1997; 75(6):696–703.
11. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes 2013; 20(1):14–21.
12. Olsson C, Holmgren S. Autonomic control of gut motility: a comparative view. Auton Neurosci 2011; 165(1):80–101.
13. Lelievre V, Favrais G, Abad C, et al. Gastrointestinal dysfunction in mice with a targeted mutation in the gene encoding vasoactive intestinal polypeptide: a model for the study of intestinal ileus and Hirschsprung's disease. Peptides 2007; 28(9):1688–1699.
14. Herszenyi L, Mihaly E, Tulassay Z. Somatostatin and the digestive system. Clinical experiences. Orv Hetil 2013; 154(39):1535–1540.
15. Anvari M, Paterson CA, Daniel EE. Role of nitric oxide mechanisms in control of pyloric motility and transpyloric flow of liquids in conscious dogs. Dig Dis Sci 1998; 43(3):506–512.
16. Kunze W, Furness J. The enteric nervous system and regulation of intestinal motility. Annu Rev Physiol 1999; 61(1):117–142.
17. Peeters TL, Janssens J, Vantrappen GR. Somatostatin and the interdigestive migrating motor complex in man. Regul Pept 1983; 5(3):209–217.
18. Achem-Karam SR, Funakoshi A, Vinik A, et al. Plasma motilin concentration and interdigestive migrating motor complex in diabetic gastroparesis: effect of metoclopramide. Gastroenterology 1985; 88(2):492–499.
19. Hall K, Diamant N, El-Sharkawy T, et al. Effect of pancreatic polypeptide on canine migrating motor complex and plasma motilin. Am J Physiol Gastrointest Liver Physiol 1983; 245(2):G178–G185.
20. Vantrappen G, Janssens J, Hellemans J, et al. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest 1977; 59(6):1158–1166.
21. Bueno L, Fioramonti J, Ruckebusch Y. Rate of flow of digesta and electrical activity of the small intestine in dogs and sheep. J Physiol 1975; 249(1):69–85.
22. Vantrappen G, Janssens J. Different meals produce different digestive motility patterns. Dig Dis Sci 1984; 29(3):219–224.
23. Miller L, Clave P, Farre R, et al. Physiology of the upper segment, body, and lower segment of the esophagus. Ann N Y Acad Sci 2013; 1300(1):261–267.
24. Hirsch DP, Holloway RH, Tytgat GN, Boeckxstaens GE. Involvement of nitric oxide in human transient lower esophageal sphincter relaxations and esophageal primary peristalsis. Gastroenterology 1998; 115(6):1374–1380.
25. Gunshefski LA, Rifley WJ, Slattery DW, et al. Somatostatin stimulation of the normal esophagus. Am J Surg 1992; 163(1):59–62.
26. Chaussade S, Michopoulos S, Sogni P, et al. Motilin agonist erythromycin increases human lower esophageal sphincter pressure by stimulation of cholinergic nerves. Dig Dis Sci 1994; 39(2):381–384.
27. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. Gastroenterology 1984; 86(6):1592–1610.
28. Chapman MJ, Nguyen NQ, Fraser RJ. Gastrointestinal motility and prokinetics in the critically ill. Curr Opin Crit Care 2007; 13(2):187–194.
29. Russell J, Bass P. Canine gastric emptying of fiber meals: influence of meal viscosity and antroduodenal motility. Am J Physiol Gastrointest Liver Physiol 1985; 249(6):G662–G667.
30. Garnier L, Mei N, Melone J. Further data on the inhibitory enterogastric reflex triggered by intestinal osmotic changes in cats. J Auton Nerv Syst 1986; 16(3):171–180.
31. Dressman JB. Comparison of canine and human gastrointestinal physiology. Pharm Res 1986; 3(3):123–131.
32. Chandler ML, Guilford G, Lawoko CR. Radiopaque markers to evaluate gastric emptying and small intestinal transit time in healthy cats. J Vet Intern Med 1997; 11(6):361–364.
33. Camilleri M, Ford M. Review article: colonic sensorimotor physiology in health, and its alteration in constipation and diarrhoeal disorders. Aliment Pharmacol Ther 1998; 12(4):287–302.
34. Fioramonti JBL. Diurnal changes in colonic motor profile in conscious dogs. Dig Dis Sci 1983; 28(3):257–264.

35. Wienbeck M, Christensen J, Weisbrodt N. Electromyography of the colon in the unanesthetized cat. Dig Dis Sci 1972; 17(4):356–362.
36. Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 1987; 317(22):1376–1382.
37. Du Moulin G, Hedley-Whyte J, Paterson D, et al. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1982; 319(8266):242–245.
38. Johnston JD, Harvey CJ, Menzies IS. Gastrointestinal permeability and absorptive capacity in sepsis. Crit Care Med 1996; 7(24):1144–1149.
39. Shimizu K, Ogura H, Asahara T, et al. Gastrointestinal dysmotility is associated with altered gut flora and septic mortality in patients with severe systemic inflammatory response syndrome: a preliminary study. Neurogastroenterol Motil 2011; 23(4):330-e157.
40. Madl CDW. Systemic consequences of ileus. Best Pract Res Clin Gastroenterol 2003; 17(3):445–456.
41. Kölbel CB, Rippel K, Klar H, et al. Esophageal motility disorders in critically ill patients: a 24-hour manometric study. Intensive Care Med 2000; 26(10):1421–1427.
42. Nind G, Chen WH, Protheroe R, et al. Mechanisms of gastroesophageal reflux in critically ill mechanically ventilated patients. Gastroenterology 2005; 128(3):600–606.
43. Dive A, Miesse C, Jamart J, et al. Duodenal motor response to continuous enteral feeding is impaired in mechanically ventilated critically ill patients. Clin Nutr 1994; 13(5):302–306.
44. Chapman M, Fraser R, Vozzo R, et al. Antro-pyloro-duodenal motor responses to gastric and duodenal nutrient in critically ill patients. Gut 2005; 54(10):1384–1390.
45. Nguyen N, Fraser R, Chapman M, et al. Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. Crit Care Med 2007; 35(1):82–88.
46. Sheth SG, LaMont JT. Toxic megacolon. Lancet 1998; 351(9101):509–513.
47. Miedema BW, Schillie S, Simmons JW, et al. Small bowel motility and transit after aortic surgery. J Vasc Surg 2002; 36(1):19–24.
48. Ritz MA, Fraser R, Tam W, et al. Impacts and patterns of disturbed gastrointestinal function in critically ill patients. Am J Gastroenterol 2000; 95(11):3044–3052.
49. Stivland T, Camilleri M, Vassallo M, et al. Scintigraphic measurement of regional gut transit in idiopathic constipation. Gastroenterology 1991; 101(1):107–115.
50. Fruhwald S, Holzer P, Metzler H. Gastrointestinal motility in acute illness. Wien Klin Wochenschr 2008; 120(1–2):6–17.
51. Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome). Dis Colon Rectum 1986; 29(3):203–210.
52. Fazel A, Verne GN. New solutions to an old problem: acute colonic pseudo-obstruction. J Clin Gastroenterol 2005; 39(1):17–20.
53. Washabau R, Hall J. Diagnosis and management of gastrointestinal motility disorders in dogs and cats. Compend Contin Educ Pract Vet 1997; 6(19):721–736.
54. Collins MT. Canine inflammatory bowel disease: current and prospective biomarkers for diagnosis and management. Compend Contin Educ Vet 2013; 35(3):E1–E7.
55. Monnig AA, Prittie JE. A review of stress-related mucosal disease. J Vet Emerg Crit Care 2011; 21(5):484–495.
56. Prittie JE. Canine parvoviral enteritis: a review of diagnosis, management, and prevention. J Vet Emerg Crit Care 2004; 14(3):167–176.
57. Mohr AJ, Leisewitz AL, Jacobson LS, et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003; 17(6):791–798.
58. Hall J, Willer R, Seim H 3rd et al. Gastric emptying of nondigestible radiopaque markers after circumcostal gastropexy in clinically normal dogs and dogs with gastric dilatation-volvulus. Am J Vet Res 1992; 53(10):1961–1965.
59. Gue M, Fioramonti D, Frexinos J, et al. Influence of acoustic stress by noise on gastrointestinal motility in dogs. Dig Dis Sci 1987; 32(12):1411–1417.
60. Takeda M, Mizutani Y, Yamano M, et al. Gastric emptying in diabetic gastroparetic dogs: effects of SK-951, a novel prokinetic agent. Pharmacology 2001; 62(1):23–28.
61. Cullen JJ, Caropreso DK, Ephgrave KS. Effect of endotoxin on canine gastrointestinal motility and transit. J Surg Res 1995; 58(1):90–95.
62. Fonda D, Gualtieri M, Scanziani E. Gastric carcinoma in the dog: a clinicopathological study of 11 cases. J Small Anim Pract 1989; 30(6):353–360.
63. Sautter J, Hanlon G. Gastric neoplasms in the dog: a report of 20 cases. J Am Vet Med Assoc 1975; 166(7):691–696.
64. Enck P, Holtmann G. Stress and gastrointestinal motility in animals: a review of the literature. Neurogastroenterol Motil 1992; 4(2):83–90.
65. Bochicchio GV, Bochicchio K, Nehman S, et al. Tolerance and efficacy of enteral nutrition in traumatic brain-injured patients induced into barbiturate coma. J Parenter Enteral Nutr 2006; 30(6):503–506.
66. Stechmiller J, Treloar DM, Derrico D, et al. Interruption of enteral feedings in head injured patients. J Neurosci Nurs 1994; 26(4):224–229.
67. Streeten D, Williams EV. Loss of cellular potassium as a cause of intestinal paralysis in dogs. J Physiol 1952; 118(2):149–170.
68. Golzarian J, Richards WO. Hypermagnesemia-induced paralytic ileus. Dig Dis Sci 1994; 39(5):1138–1142.
69. Kowalewski K, Kolodej A. Myoelectrical and mechanical activity of isolated canine stomach perfused in vitro with fluorocarbon. Role of glucose, phosphate, calcium and strontium in the perfusate. Pharmacology 1978; 16(5):247–258.
70. Sternini C, Patierno S, Selmer IS, et al. The opioid system in the gastrointestinal tract. Neurogastroenterol Motil 2004; 16(s2):3–16.
71. Bueno L, Fiaramonti J, Honde C, Fargeas MJ, Primi MP. Central and peripheral control of gastroinestinal and colonic motility by endogenous opiates in conscious dogs. Gastroenterology 1985; 88(2):549–556.
72. Kurz A, Sessler DI. Opioid-induced bowel dysfunction. Drugs 2003; 63(7):649–671.
73. Yuan CS, Foss JF. Methylnaltrexone: investigation of clinical applications. Drug Dev Res 2000; 50(2):133–141.
74. Fruhwald S, Scheidl S, Toller W, et al. Low potential of dobutamine and dopexamine to block intestinal peristalsis as compared with other catecholamines. Crit Care Med 2000; 28(8):2893–2897.
75. Marzio L, Neri M, Pieramico O, et al. Dopamine interrupts gastrointestinal fed motility pattern in humans. Dig Dis Sci 1990; 35(3):327–332.
76. Cullen L. Medetomidine sedation in dogs and cats: a review of its pharmacology, antagonism and dose. Br Vet J 1996; 152(5):519–535.
77. Iirola T, Vilo S, Aantaa R, et al. Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers. Br J Anaesth 2011; 106(4):522–527.
78. James A, Ryan J, Parkman H. Effects of clonidine and tricyclic antidepressants on gastric smooth muscle contractility. Neurogastroenterol Motil 2004; 16(2):143–153.
79. Horowitz M, Edelbroek M, Fraser R, et al. Disordered gastric motor function in diabetes mellitus: recent insights into prevalence, pathophysiology, clinical relevance, and treatment. Scand J Gastroenterol 1991; 26(7):673–684.
80. Abrahamsson H. Gastrointestinal motility disorders in patients with diabetes mellitus. J Intern Med 1995; 237(4):403–409.
81. Nguyen N, Ching K, Fraser R. The relationship between blood glucose control and intolerance to enteral feeding during critical illness. Intensive Care Med 2007; 33(12):2085–2092.
82. Mori A, Lee P, Sako T, et al. Successful intensive insulin treatment of type 1 diabetic dogs leads to restoration of peripheral leukocyte insulin signaling gene expression and enzyme activities. J Vet Med Sci 2009; 71(8):1017–1026.
83. Lam S, Nguyen N, Ching K, et al. Gastric feed intolerance is not increased in critically ill patients with type II diabetes. Intensive Care Med 2007; 33(1):1740–1745.
84. Smith J, Kelly KA, Weinshilboum RM. Pathophysiology of postoperative ileus. Arch Surg 1977; 112(2):203–209.

85. Fuortes M, Blank M, Scalea T, et al. Release of vasoactive intestinal peptide during hyperdynamic sepsis in dogs. Surgery 1988; 104(5):894–898.
86. Cullen J, Caropreso D, Ephgrave K. Effect of endotoxin on canine gastrointestinal motility and transit. J Surg Res 1995; 58(1): 90–95.
87. Mattei P, Rombeau JL. Review of the pathophysiology and management of postoperative ileus. World J Surg 2006; 30(8):1382–1391.
88. Ritz MA, Fraser R, Edwards N, et al. Delayed gastric emptying in ventilated critically ill patients: measurement by 13C-octanoic acid breath test. Crit Care Med 2001; 29(9):1744–1749.
89. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. Crit Care Med 1999; 27(8):1447–1453.
90. Schrenk Tv, DerHerr G, Matsui U. Hydrogen breath tests: can these non-invasive function tests be used in ICU patients? AINS 1998; 33(1):624–631.
91. Atherton S, White D. Stomach as source of bacteria colonising respiratory tract during artificial ventilation. Lancet 1978; 312(8097):968–969.
92. Zacuto AC, Marks SL, Osborn J, et al. The influence of esomeprazole and cisapride on gastroesophageal reflux during anesthesia in dogs. J Vet Intern Med 2012; 26(3):518–525.
93. Glazer A, Walters P. Esophagitis and esophageal strictures. Compend Contin Educ Vet 2008; 30(5):281–292.
94. Wilson DV, Walshaw R. Postanesthetic esophageal dysfunction in 13 dogs. J Am Anim Hosp Assoc 2004; 40(6):455–460.
95. Galatos AD, Raptopoulos D. Gastro-oesophageal reflux during anaesthesia in the dog: the effect of preoperative fasting and premedication. Vet Rec 1995; 137(19):479–483.
96. Kogan DA, Johnson LR, Jandrey KE, et al. Clinical, clinicopathologic, and radiographic findings in dogs with aspiration pneumonia: 88 cases (2004–2006). J Am Vet Med Assoc 2008; 233(11):1742–1747.
97. Han E, Broussard J, Baer KE. Feline esophagitis secondary to gastroesophageal reflux disease: clinical signs and radiographic, endoscopic, and histopathological findings. J Am Anim Hosp Assoc 2003; 39(2):161–167.
98. Quigley E. Critical care dysmotility: abnormal foregut motor function in the ICU/ITU patient. Gut 2005; 54(10):1351–1352.
99. Alverdy JC, Chang EB. The re-emerging role of the intestinal microflora in critical illness and inflammation: why the gut hypothesis of sepsis syndrome will not go away. J Leukoc Biol 2008; 83(3):461–466.
100. Papoff P, Ceccarelli G, d'Ettorre G, et al. Gut microbial translocation in critically ill children and effects of supplementation with pre- and pro biotics. Int J Microbiol 2012; 1(151393):1–8.
101. Alexander JW, Boyce ST, Babcock GF, et al. The process of microbial translocation. Ann Surg 1990; 212(4):496–510.
102. Shimizu K, Ogura H, Goto M, et al. Altered gut flora and environment in patients with severe SIRS. J Trauma Acute Care Surg 2006; 60(1):126–133.
103. Marshall JC. Gastrointestinal flora and its alterations in critical illness. Curr Opin Clin Nutr Metab Care 1999; 2(5):405–411.
104. Smith S, Sande A. Measurement of intra-abdominal pressure in dogs and cats. J Vet Emerg Crit Care 2012; 22(5):530–544.
105. Holodinsky JK, Roberts DJ, Ball CG, et al. Risk factors for intra-abdominal hypertension and abdominal compartment syndrome among adult intensive care unit patients: a systematic review and meta-analysis. Crit Care 2013; 17(5):R249 1–15.
106. Van Noord BA, Roffey P, Thangathurai D. Abdominal compartment syndrome following opioid-induced postoperative ileus. J Clin Anesth 2013; 25(2):146–149.
107. Madl C, Druml W. Gastrointestinal disorders of the critically ill. Systemic consequences of ileus. Best Pract Res Clin Gastroenterol 2003; 17(3):445–456.
108. Chapman MJ, Nguyen NQ, Deane AM. Gastrointestinal dysmotility: evidence and clinical management. Curr Opin Clin Nutr Metab Care 2013; 16(2):209–216.
109. Kreymann K, Berger M, Deutz N, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 2006; 25(2):210–223.
110. Yu MK, Freeman LM, Heinze CR, et al. Comparison of complication rates in dogs with nasoesophageal versus nasogastric feeding tubes. J Vet Emerg Crit Care 2013; 23(3):300–304.
111. Holahan M, Abood S, Hauptman J, et al. Intermittent and continuous enteral nutrition in critically ill dogs: a prospective randomized trial. J Vet Intern Med 2010; 24(3):520–526.
112. Btaiche IF, Chan LN, Pleva M, et al. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. Nutr Clin Pract 2010; 25(1):32–49.
113. Wyse CA, McLellan J, Dickie AM, et al. A review of methods for assessment of the rate of gastric emptying in the dog and cat: 1998–2002. J Vet Intern Med 2003; 17(5):609–621.
114. Miyabayashi T, Morgan JP. Gastric emptying in the normal dog a contrast radiographic technique. Vet Radiol Ultrasound 1984; 25(4):187–191.
115. Burns J, Fox S. The use of a barium meal to evaluate total gastric emptying time in the dog. Vet Radiol Ultrasound 1986; 27(6):169–172.
116. Steyn PF, Twedt D, Toombs W. The scintigraphic evaluation of solid phase gastric emptying in normal cats. Vet Radiol Ultrasound 1995; 36(4):327–331.
117. Lester NV, Roberts GD, Newell SM, et al. Assessment of barium impregnated polyethylene spheres (BIPS) as a measure of solid-phase gastric emptying in normal dogs—comparison to scintigraphy. Vet Radiol Ultrasound 1999; 40(5):465–471.
118. Sparkes A, Papasouliotis K, Barr F, et al. Reference ranges for gastrointestinal transit of barium-impregnated polyethylene spheres in healthy cats. J Small Anim Pract 1997; 38(8):340–343.
119. Hornof WJ, Koblik PD, Strombeck DR, et al. Scintigraphic evaluation of solid-phase gastric emptying in the dog. Vet Radiol Ultrasoun 1989; 30(6):242–248.
120. Tsukamoto A, Ohno K, Tsukagoshi T, et al. Real-time ultrasonographic evaluation of canine gastric motility in the postprandial state. J Vet Med Sci 2011; 73(9):1133–1138.
121. Chalmers AF, Kirton R, Wyse CA, et al. Ultrasonographic assessment of the rate of solid-phase gastric emptying in dogs. Vet Rec 2005; 157(21):649–652.
122. McLellan J, Wyse CA, Dickie A, et al. Comparison of the carbon 13-labeled octanoic acid breath test and ultrasonography for assessment of gastric emptying of a semisolid meal in dogs. Am J Vet Res 2004; 65(11):1557–1562.
123. An YJ, Lee H, Chang D, et al. Application of pulsed Doppler ultrasound for the evaluation of small intestinal motility in dogs. J Vet Sci 2001; 2(1):71–74.
124. Calletti T, Gaiani S, Labb G. Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology 1985; 89(1):752–759.
125. Bowman LC, Williams R, Sanders M, et al. Algorithm for nutritional support: experience of the metabolic and infusion support service of St. Jude Children's Research Hospital. Int J Cancer 1998; 78(S11):76–80.
126. Wøien H, Bjørk IT. Nutrition of the critically ill patient and effects of implementing a nutritional support algorithm in ICU. J Clin Nurs 2006; 15(2):168–177.
127. De Jonghe B, Appere-De-Vechi C, Fournier M, et al. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001; 29(1):8–12.
128. Iwanaga Y, Wen J, Thollander MS, et al. Scintigraphic measurement of regional gastrointestinal transit in the dog. Am J Physiol Gastrointest Liver Physiol 1998; 275(5):G904–G910.
129. Schmitz S, Failing K, Neiger R. Solid phase gastric emptying times in the dog measured by 13C-sodium-acetate breath test and 99m technetium radioscintigraphy. Tierarztl Prax Kleintiere 2010; 38 (1):211–216.
130. Papasouliotis K, Gruffydd-Jones T, Sparkes A, et al. A comparison of orocaecal transit times assessed by the breath hydrogen test and the sulphasalazine/sulphapyridine method in healthy beagle dogs. Res Vet Sci 1995; 58(3):263–267.
131. Hansen M. Small intestinal manometry. Physiol Res 2002; 51(6):541–556.

132. Kempf J, Heinrich H, Reusch CE, et al. Evaluation of esophageal high-resolution manometry in awake and sedated dogs. Am J Vet Res 2013; 74(6):895–900.
133. Meyer JH, Dressman J, Fink A, et al. Effect of size and density on canine gastric emptying of nondigestible solids. Gastroenterology 1985; 89(1):805–813.
134. Patak MA, Froehlich JM, von Weymarn C, et al. Non-invasive measurement of small-bowel motility by MRI after abdominal surgery. Gut 2007; 56(7):1023–1025.
135. Kempf J, Lewis F, Reusch CE, et al. High-resolution manometric evaluation of the effects of cisapride and metoclopramide hydrochloride administered orally on lower esophageal sphincter pressure in awake dogs. Am J Vet Res 2014; 75(4):361–366.
136. Will K, Nolte I, Zentek J. Early enteral nutrition in young dogs suffering from haemorrhagic gastroenteritis. J Vet Med A Physiol Pathol Clin Med 2005; 52(7):371–376.
137. Brunetto MA, Gomes MO, Andre MR, et al. Effects of nutritional support on hospital outcome in dogs and cats. J Vet Emerg Crit Care 2010; 20(2):224–231.
138. Liu DT, Brown DC, Silverstein DC. Early nutritional support is associated with decreased length of hospitalization in dogs with septic peritonitis: a retrospective study of 45 cases (2000–2009). J Vet Emerg Crit Care 2012; 22(4):453–459.
139. Hadfield RJ, Sinclair D, Houldsworth PE. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med 1995; 152(5):1545–1548.
140. Li J, Kudsk K, Gocinski B. Effects of parenteral and enteral nutrition on gut associated lymphoid tissue. J Trauma 1995; 39(1):44–52.
141. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001; 29(12):2264–2270.
142. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006; 129(4):960–967.
143. Goggin J, Hoskinson J, Butine MD, et al. Scintigraphic assessment of gastric emptying in canned and dry diets in healthy cats. Am J Vet Res 1998; 59(4):388–392.
144. Davies AR, Morrison SS, Bailey MJ, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med 2012; 40(8):2342–2348.
145. White H, Sosnowski K, Tran K, et al. A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated intensive care patients. Crit Care 2009; 13(6):R187.
146. Ho KM, Dobb GJ, Webb SA. A comparison of early gastric and postpyloric feeding in critically ill patients: a meta-analysis. Intensive Care Med 2006; 32(5):639–649.
147. Mythen M, Webb A. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995; 130(4):423–429.
148. Moore F, Feliciano D, Andrassy R, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 1992; 216(2):172.
149. Radhakrishnan R, Xue H, Moore-Olufemi S, et al. Hypertonic saline resuscitation prevents hydrostatically induced intestinal edema and ileus. Crit Care Med 2006; 34(6):1713–1717.
150. Moore-Olufemi SD, Xue H, Attuwaybi BO, et al. Resuscitation-induced gut edema and intestinal dysfunction. J Trauma Acute Care Surg 2005; 58(2):264–270.
151. Radhakrishnan RS, Xue H, Weisbrodt N, et al. Resuscitation-induced intestinal edema decreases the stiffness and residual stress of the intestine. Shock 2005; 24(2):165–170.
152. Uray KS, Wright Z, Kislitsyna K, et al. Nuclear factor-[kappa] B activation by edema inhibits intestinal contractile activity. Crit Care Med 2010; 38(3):861–870.
153. Moore-Olufemi SD, Xue H, Allen SJ, et al. Inhibition of intestinal transit by resuscitation-induced gut edema is reversed by L-NIL. J Surg Res 2005; 129(1):1–5.
154. Chowdhury AH, Lobo DN. Fluids and gastrointestinal function. Curr Opin Clin Nutr Metab Care 2011; 14(5):469–476.
155. Walsh SR, Tang TY, Farooq N, et al. Perioperative fluid restriction reduces complications after major gastrointestinal surgery. Surgery 2008; 143(4):466–468.
156. Glick YA, Wilson LD, Aiello J. Hematocrit and metabolic changes caused by varied resuscitation strategies in a canine model of hemorrhagic shock. Am J Emerg Med 2002; 20(4):303–309.
157. Radhakrishnan RS, Shah SK, Lance SH, et al. Hypertonic saline alters hydraulic conductivity and up-regulates mucosal/submucosal aquaporin 4 in resuscitation-induced intestinal edema. Crit Care Med 2009; 37(11):2946–2952.
158. Vather R, Bissett I. Management of prolonged post-operative ileus: evidence-based recommendations. ANZ J Surg 2013; 83(5):319–324.
159. Thompson M, Magnuson B. Management of postoperative ileus. Orthopedics 2012; 35(3):213–217.
160. Waldhausen JH, Schirmer BD. The effect of ambulation on recovery from postoperative ileus. Ann Surg 1990; 212(6):671–677.
161. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367(9522):1618–1625.
162. Hannon B, Zimmermann C, Bryson JR. The role of fentanyl in refractory opioid-related acute colonic pseudo-obstruction. J Pain Symptom Manage 2013; 45(3):e1-e3.
163. Nakamura A, Hasegawa M, Ito H, et al. Distinct relations among plasma concentrations required for different pharmacological effects in oxycodone, morphine, and fentanyl. J Pain Palliat Care Pharmacother 2011; 25(4):318–334.
164. Narabayashi M, Saijo Y, Takenoshita S, et al. Opioid rotation from oral morphine to oral oxycodone in cancer patients with intolerable adverse effects: an open-label trial. Jpn J Clin Oncol 2008; 38(4):296–304.
165. Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother 2007; 41(6):921–928.
166. Branford R, Droney J, Ross JR. Opioid genetics: the key to personalized pain control? Clin Genet 2012; 82(4):301–310.
167. Holte K, Kehlet H. Postoperative ileus: progress towards effective management. Drugs 2002; 62(18):2603–2615.
168. Jorgensen H, Wetterslev J, Moiniche S, et al. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000; 1(4):CD001893.
169. Rawlinson A, Kitchingham N, Hart C, et al. Mechanisms of reducing postoperative pain, nausea and vomiting: a systematic review of current techniques. Evid Based Med 2012; 17(3):75–80.
170. Chen SF, Li YQ, He FY. Effect of *Saussurea lappa* on gastric functions. Zhongguo Zhong Xi Yi Jie He Za Zhi 1994; 14(7):406–408.
171. Chen X, Ran R. Rhubarb decoction prevents intestinal bacterial translocation during necrotic pancreatitis. Hua Xi Yi Ke Da Xue Xue Bao 1996; 27(4):418–421.
172. Lin X, Liang J, Ren J, et al. Electrical stimulation of acupuncture points enhances gastric myoelectrical activity in humans. Am J Gastroenterol 1997; 92(9):1527–1530.
173. Balestrini JL, Tsuchida D, Fukuda H, et al. Acupuncture accelerates delayed gastrointestinal transit after abdominal surgery in conscious rats. Scand J Gastroenterol 2005; 40(6):734–735.
174. Dai JL, Ren ZJ, Fu ZM, et al. Electroacupuncture reversed the inhibition of intestinal peristalsis induced by intrathecal injection of morphine in rabbits. Chin Med J 1993; 106(3):220–224.
175. Mastropaolo M, Zizzo MG, Auteri M, et al. Arginine vasopressin, via activation of post-junctional V1 receptors, induces contractile effects in mouse distal colon. Regul Pept 2013; 187(1):29–34.
176. Ward SM, Bayguinov OP, Lee HK, et al. Excitatory and inhibitory actions of vasopressin on colonic excitation-contraction coupling in dogs. Gastroenterology 1997; 113(4):1233–1245.
177. Qin J, Liu K, Wang PS, et al. V1 receptor in ENS mediates the excitatory effect of vasopressin on circular muscle strips of gastric body in vitro in rats. Regul Pept 2009; 157(1–3):32–36.
178. Bridges RJ, Nell G, Rummel W. Influence of vasopressin and calcium on electrolyte transport across isolated colonic mucosa of the rat. J Physiol 1983; 338(1):463–475.
179. Mann R, Bell C. Distribution and origin of aminergic neurones in dog small intestine. J Auton Nerv Syst 1993; 43(2):107–115.

180. Willems J, Buylaert W, Lefebvre R, et al. Neuronal dopamine receptors on autonomic ganglia and sympathetic nerves and dopamine receptors in the gastrointestinal system. Pharmacol Rev 1985; 37(2):165–216.
181. Wiley J, Owyang C. Dopaminergic modulation of rectosigmoid motility: action of domperidone. J Pharmacol Exp Ther 1987; 242(2):548–551.
182. Patterson D, Abell T, Rothstein R, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol 1999; 94(5):1230–1234.
183. Orihata M, Sarna SK. Contractile mechanisms of action of gastroprokinetic agents: cisapride, metoclopramide, and domperidone. Am J Physiol Gastrointest Liver Physiol 1994; 266(4):G665–G676.
184. Depoortère R, Barret-Grévoz C, Bardin L, et al. Apomorphine-induced emesis in dogs: differential sensitivity to established and novel dopamine D2/5-HT(1A) antipsychotic compounds. Eur J Pharmacol 2008; 597(1):34–38.
185. Camilleri M. Serotonin in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes 2009; 16(1):53–59.
186. Hasler WL. Serotonin and the GI tract. Curr Gastroenterol Rep 2009; 11(5):383–391.
187. Prins N, van Der Grijn A, Lefebvre R, et al. 5-HT4 receptors mediating enhancement of contractility in canine stomach; an in vitro and in vivo study. Br J Clin Pharmacol 2001; 132(8):1941–1947.
188. McCallum RW, Prakash C, Campoli-Richards DM, et al. Cisapride. Drugs 1988; 36(6):652–681.
189. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord 1998; 51(3):215–235.
190. Woosley KP. The problem of gastric atony. Clin Tech Small Anim Pract 2004; 19(1):43–48.
191. Burger DM, Wiestner T, Hubler M, et al. Effect of anticholinergics (atropine, glycopyrrolate) and prokinetics (metoclopramide, cisapride) on gastric motility in beagles and labrador retrievers. J Vet Med A Physiol Pathol Clin Med 2006; 53(2):97–107.
192. Gullikson GW, Loeffler RF, Virina MA. Relationship of serotonin-3 receptor antagonist activity to gastric emptying and motor-stimulating actions of prokinetic drugs in dogs. J Pharmacol Exp Ther 1991; 258(1):103–110.
193. Fraser R, Horowitz M, Maddox A, et al. Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis—effects of cisapride. Gut 1994; 35(2):172–178.
194. Schuurkes J, Akkermans L, Van Nueten J. Stimulating effects of cisapride on antroduodenal motility in the conscious dog. Gastrointest Motil 1983; 95–102.
195. Reboa G, Arnulfo G, Frascio M, et al. Colon motility and coloanal reflexes in chronic idiopathic constipation. Effects of a novel enterokinetic agent cisapride. Eur J Clin Pharmacol 1984; 26(6):745–748.
196. Prokić B, Todorović V, Mitrović O, et al. Ethiopathogenesis, diagnosis and therapy of acquired megacolon in dogs. Acta Vet 2010; 60(2–3):273–284.
197. White D. Managing the constipated cat. Companion Anim 2008; 13(7):21–28.
198. Wysowski DK, Corken A, Gallo-Torres H, et al. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001; 96(6):1698–1703.
199. Chain AS, Dubois VF, Danhof M, et al. Identifying the translational gap in the evaluation of drug-induced QTc interval prolongation. Br J Clin Pharmacol 2013; 76(5):708–724.
200. Hall JAWR, Seim HB. Gastric emptying of nondigestible radioopaque markers after circumcostal gastropexy in clinically normal dogs and dogs with gastric dilatation-volvulus. Am J Vet Res 1992; 53(10):1961–1965.
201. Mangel A, Stavorski J, Pendleton R. Effects of bethanechol, metoclopramide, and domperidone on antral contractions in cats and dogs. Digestion 1983; 28(4):205–209.
202. Wilson D, Evans T, Mauer W. Influence of metoclopramide on gastroesophageal reflux in anesthetized dogs. Am J Vet Res 2006; 67(1):26–31.
203. Schwach-Abdellaoui KMM, Schneider M, Boisramc B, et al. Controlled delivery of metoclopramide using an injectable semi-solid poly(ortho ester) for veterinary application. Int J Pharm 2002; 248(1–2):31–37.
204. Radwanski NE, Cerundolo R, Shofer FS, et al. Effects of powdered whole grapefruit and metoclopramide on the pharmacokinetics of cyclosporine in dogs. Am J Vet Res 2011; 72(5):687–693.
205. Kandler D, Lisander B. Analgesic action of metoclopramide in prosthetic hip surgery. Acta Anaesth Scand 1993; 37(1):49–53.
206. Jo YY, Kim YB, Yang MR, et al. Extrapyramidal side effects after metoclopramide administration in a post-anesthesia care unit—a case report. Korean J Anesthesiol 2012; 63(3):274–276.
207. Kamin J, Manwani S, Hughes D. Emergency psychiatry: extrapyramidal side effects in the psychiatric emergency service. Psychiatr Serv 2000; 51(3):287–289.
208. Herzog TJ, Coleman RL, Guerrieri JP Jr, et al. A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. Am J Obstet Gynecol 2006; 195(2):445–453.
209. Banh HL, MacLean C, Topp T, et al. The use of tegaserod in critically ill patients with impaired gastric motility. Clin Pharmacol Ther 2005; 77(6):583–586.
210. Curran MP, Robinson DM. Mosapride. Drugs 2008; 68(7):981–991.
211. Lim HC, Kim JH, Youn YH, et al. Effects of the addition of mosapride to gastroesophageal reflux disease patients on proton pump inhibitor: a prospective randomized, double-blind study. J Neurogastroenterol Motil 2013; 19(4):495–502.
212. Briejer MR, Bosmans JP, Van Daele P, et al. The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. Eur J Pharmacol 2001; 423(1):71–83.
213. Briejer MR, Prins NH, Schuurkes JA. Effects of the enterokinetic prucalopride (R093877) on colonic motility in fasted dogs. Neurogastroenterol Motil 2001; 13(5):465–472.
214. Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008; 358(22):2344–2354.
215. Tsukamoto A, Ohno K, Maeda S, et al. Prokinetic effect of the 5-HT4R agonist mosapride on canine gastric motility. J Vet Med Sci 2011; 73(12):1635.
216. Fioramonti J, Million M, Bueno L. Investigations on a 5-HT4 agonist (SDZ HTF 919) and its main metabolite in conscious dogs: effects on gastrointestinal motility and impaired gastric emptying. Gastroenterology 1998; 114(4):G3103.
217. Weber E, Braun E, Forgiarini P, et al. Tegaserod normalizes opioid-induced bowel dysfunction in dogs. Gastroenterology 2003; 124(4):A571–A571.
218. Nguyen A, Camilleri M, Kost LJ, et al. SDZ HTF 919 stimulates canine colonic motility and transit in vivo. J Pharmacol Exp Ther 1997; 280(3):1270–1276.
219. Lippold B, Hildebrand J, Straub R. Tegaserod (HTF 919) stimulates gut motility in normal horses. Equine Vet J 2004; 36(7):622–627.
220. Delco ML, Nieto JE, Craigmill AL, et al. Pharmacokinetics and in vitro effects of tegaserod, a serotonin 5-hydroxytryptamine 4 (5-HT4) receptor agonist with prokinetic activity in horses. Vet Ther 2007; 8(1):77–87.
221. De Smet B, Mitselos A, Depoortere I. Motilin and ghrelin as prokinetic drug targets. Pharmacol Ther 2009; 123(2):207–223.
222. Ludtke FE, Muller H, Golenhofen K. Direct effects of motilin on isolated smooth muscle from various regions of the human stomach. Pflugers Arch 1989; 414(5):558–563.
223. Vantrappen G, Janssens J, Peeters TL, Bloom SR, Christofides ND, Hellemans J. Motilin and the interdigestive migrating motor complex in man. Dig Dis Sci 1979; 24(7):497–500.
224. Adachi HTN, Hayashi S. Mechanism of the excitatory action of motilin on isolated rabbit intestine. Gastroenterology 1981; 80(4):783–788.

225. Itoh Z, Honda R, Hiwatashi K, et al. Motilin-induced mechanical activity in the canine alimentary tract. Scand J Gastroenterol Suppl 1976; 39(1):93–110.
226. Peeters TL. Potential of ghrelin as a therapeutic approach for gastrointestinal motility disorders. Curr Opin Pharmacol 2006; 6(6):553–558.
227. Weber F Jr, Richards R, McCallum R. Erythromycin: a motilin agonist and gastrointestinal prokinetic agent. Am J Gastroenterol 1993; 88(4):485–490.
228. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. J Antimicrob Chemother 2007; 59(3):347–358.
229. Nguyen NQ, Chapman MJ, Fraser RJ, et al. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. Crit Care Med 2007; 35(2):483–489.
230. Chapman MJ, Fraser RJ, Kluger MT, et al. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. Crit Care Med 2000; 28(7):2334–2337.
231. Boivin MA, Levy H. Gastric feeding with erythromycin is equivalent to transpyloric feeding in the critically ill. Crit Care Med 2001; 29(10):1916–1919.
232. Reignier J, Bensaid S, Perrin-Gachadoat D, et al. Erythromycin and early enteral nutrition in mechanically ventilated patients. Crit Care Med 2002; 30(6):1237–1241.
233. Pilot MA. Macrolides in roles beyond antibiotic therapy. Br J Surg 1994; 81(10):1423–1429.
234. Pilot M, Ritchie H, Thompson H, et al. Alterations in gastrointestinal motility associated with erythromycin. Br J Clin Pharmacol 1984; 81(1):168–174.
235. Sarna SK, Gonzalez A, Ryan RP. Enteric locus of action of prokinetics: ABT-229, motilin, and erythromycin. Am J Physiol Gastrointest Liver Physiol 2000; 278(5):G744–752.
236. Sako F, Marui S, Inatomi N, et al. EM574, an erythromycin derivative, improves delayed gastric emptying of semi-solid meals in conscious dogs. Eur J Pharmacol 2000; 395(2):165–172.
237. Gintant GA, Limberis JT, McDermott JS, et al. The canine Purkinje fiber: an in vitro model system for acquired long QT syndrome and drug-induced arrhythmogenesis. J Cardiovasc Pharmacol 2001; 37(5):607–618.
238. Potter TG, Snider KR. Azithromycin for the treatment of gastroparesis. Ann Pharmacother 2013; 47(3):411–415.
239. Chini P, Toskes PP, Waseem S, et al. Effect of azithromycin on small bowel motility in patients with gastrointestinal dysmotility. Scand J Gastroenterol 2012; 47(4):422–427.
240. Abrahamsson H. Treatment options for patients with severe gastroparesis. Gut 2007; 56(6):877–883.
241. Trudel L, Bouin M, Tomasetto C, et al. Two new peptides to improve post-operative gastric ileus in dog. Peptides 2003; 24(4):531–534.
242. Onoma M, Yogo K, Ozaki K, et al. Oral mitemcinal (GM-611), an erythromycin-derived prokinetic, accelerates normal and experimentally delayed gastric emptying in conscious dogs. Clin Exp Pharmacol Physiol 2008; 35(1):35–42.
243. Bertaccini G, Coruzzi G. An update on histamine H3 receptors and gastrointestinal functions. Dig Dis Sci 1995; 40(9):2052–2063.
244. Bertaccini G, Coruzzi G, Poli E. Review article: the histamine H3-receptor: a novel prejunctional receptor regulating gastrointestinal function. Aliment Pharmacol Ther 1991; 5(6):585–591.
245. Poli E, Pozzoli C, Coruzzi G. Role of histamine H(3) receptors in the control of gastrointestinal motility. An overview. J Physiol Paris 2001; 95(1–6):67–74.
246. Peters LJ, Kovacic JP. Histamine: metabolism, physiology, and pathophysiology with applications in veterinary medicine. J Vet Emerg Crit Care 2009; 19(4):311–328.
247. Sander LE, Lorentz A, Sellge G, et al. Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract. Gut 2006; 55(4):498–504.
248. Ohira Y, Hanyu N, Aoki T, et al. Effects of various histamine H2-receptor antagonists on gastrointestinal motility and gastric emptying. J Smooth Muscle Res 1993; 29(4):131–142.
249. Favarato E, Souza M, Costa P, et al. Evaluation of metoclopramide and ranitidine on the prevention of gastroesophageal reflux episodes in anesthetized dogs. Res Vet Sci 2012; 93(1):466–467.
250. Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manage 2008; 35(1):103–113.
251. Morita K, North R. Opiates and enkephalin reduce the excitability of neuronal processes. Neuroscience 1981; 6(10):1943–1951.
252. Alan North R, Henderson G. Action of morphine on guinea-pig myenteric plexus and mouse vas deferens studied by intracellular recording. Life Sci 1975; 17(1):63–66.
253. Zimmerman DM, Gidda JS, Cantrell BE, et al. Discovery of a potent, peripherally selective trans-3, 4-dimethyl-4-(3-hydroxyphenyl) piperidine opioid antagonist for the treatment of gastrointestinal motility disorders. J Med Chem 1994; 37(15):2262–2265.
254. Meerveld GV, Gardner C, Little P, et al. Preclinical studies of opioids and opioid antagonists on gastrointestinal function. Neurogastroenterol Motil 2004; 16(s2):46–53.
255. Udeh E, Goldman M. Alvimopan: a peripherally selective opioid mu receptor antagonist. Formulary 2005; 40(6):176–183.
256. Meissner W, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. Crit Care Med 2003; 31(3):776–780.
257. Schmidt WK. Alvimopan (ADL 8–2698) is a novel peripheral opioid antagonist. Am J Surg 2001; 182(5):S27–S38.
258. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting μ 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(4):728.
259. Sanz Rubiales A, del Valle Rivero ML. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008; 359(10):1070–1071.
260. Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain 2013; 154(9):1542–1550.
261. Tsuruda PR, Vickery RG, Long DD, et al. The in vitro pharmacological profile of TD-1211, a neutral opioid receptor antagonist. Naunyn Schmiedebergs Arch Pharmacol 2013; 386(6):479–491.
262. Yuan Y, Stevens DL, Braithwaite A, et al. 6beta-N-heterocyclic substituted naltrexamine derivative NAP as a potential lead to develop peripheral mu opioid receptor selective antagonists. Bioorg Med Chem Lett 2012; 22(14):4731–4734.
263. Wade PR, Palmer JM, McKenney S, et al. Modulation of gastrointestinal function by MuDelta, a mixed micro opioid receptor agonist/micro opioid receptor antagonist. Br J Pharmacol 2012; 167(5):1111–1125.
264. Gale S, Croasdell G. 28th Annual JPMorgan Healthcare Conference—Exelixis and Nektar Therapeutics. IDrugs 2010; 13(3):139–141.
265. Johanson JF, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol 2008; 103(1):170–177.
266. Moeser AJ, Nighot PK, Engelke KJ, et al. Recovery of mucosal barrier function in ischemic porcine ileum and colon is stimulated by a novel agonist of the ClC-2 chloride channel, lubiprostone. Am J Physiol Gastrointest Liver Physiol 2007; 292(2):G647–G656.
267. Morton MF, Barrett TD, Yan W, et al. 3-[5-(3,4-Dichloro-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-2-m-tolyl-propio nate (JNJ-17156516), a novel, potent, and selective cholecystokinin 1 receptor antagonist: in vitro and in vivo pharmacological comparison with dexloxiglumide. J Pharmacol Exp Ther 2007; 323(2):562–569.
268. Schwizer W, Borovicka J, Kunz P, et al. Role of cholecystokinin in the regulation of liquid gastric emptying and gastric motility in humans: studies with the CCK antagonist loxiglumide. Gut 1997; 41(4):500–504.
269. Trudgill NJ, Hussain FN, Moustafa M, et al. The effect of cholecystokinin antagonism on postprandial lower oesophageal sphincter function in asymptomatic volunteers and patients with reflux disease. Aliment Pharmacol Ther 2001; 15(9):1357–1364.

270. Gale J. The use of novel promotility and prosecretory agents for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. Adv Ther 2009; 26(5):519–530.
271. Gonzalez-Martinez MA, Ortiz-Olvera NX, Mendez-Navarro J. Novel pharmacological therapies for management of chronic constipation. J Clin Gastroenterol 2014; 48(1):21–28.
272. Gillberg PG, Dahlström M, Starke I, et al. The IBAT inhibition by A3309-A potential mechanism for the treatment of constipation. Gastroenterology 2010; 5(Suppl 1):224–232.
273. Simren M, Bajor A, Gillberg PG, et al. Randomised clinical trial: the ileal bile acid transporter inhibitor A3309 vs. placebo in patients with chronic idiopathic constipation—a double-blind study. Aliment Pharmacol Ther 2011; 34(1):41–50.

