

# 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 radionuclide scintigraphy; 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. Prokinetic 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 prophylactic therapy is recommended in high-risk patients, however, no consensus exists regarding optimal timing of initiating prophylactic 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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3,4</sup> and it has been characterized by inhibition of forward GI motility, and less frequently, hypermotility.<sup>4</sup> 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.<sup>5,6</sup>

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 ill 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).**<sup>2,4,7</sup> Motor neurons in the GI wall respond similarly across many species and are **excited by substances such as acetylcholine (ACh),<sup>8</sup> tachykinins (particularly substance P and neurokinin A),<sup>9,10</sup> and serotonin (5-hydroxytryptamine [5-HT]),<sup>11,12</sup> and inhibited by peptides, including vasoactive intestinal peptide (VIP),<sup>13</sup> somatostatin,<sup>14</sup> nitric oxide (NO),<sup>15</sup> and gamma-aminobutyric acid (GABA).<sup>12</sup>** 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.**<sup>16</sup> Regulation of the MMC is achieved by the ENS and **modulated directly by regulatory peptides including somatostatin,<sup>17</sup> motilin,<sup>18</sup> and pancreatic polypeptide.**<sup>19</sup> 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.<sup>20,21</sup> 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.**<sup>5</sup> 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.<sup>22</sup> The MMC is then replaced by the fed pattern of activity, or digestive motility, which consists of accommodation, stationary motility, and propulsive peristalsis.<sup>7</sup>

Esophageal motility is controlled via different mechanisms in both the smooth and striated muscle of the esophagus.<sup>23</sup> 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.<sup>1</sup> Neurohormonal control of esophageal motility is poorly characterized, but several hormonal influences have been described, including NO,<sup>24</sup> somatostatin,<sup>25</sup> and motilin.<sup>26</sup>

**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.<sup>15,27</sup> 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.<sup>28</sup> 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.<sup>27,29</sup> 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.<sup>30</sup>

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.<sup>2</sup> Propagation velocities of peristaltic waves lead to an average small intestinal transit time of 3–5 hours in healthy dogs<sup>31</sup> and 2–3 hours in healthy cats.<sup>32</sup> 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.<sup>33–35</sup>

### 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).<sup>5</sup> Common complications in patients with GIDM include aspiration pneumonia,<sup>36,37</sup> esophagitis, feeding difficulties,<sup>3</sup> increased risk of bacterial translocation and sepsis,<sup>38,39</sup> and increased intra-abdominal pressure (IAP).<sup>40</sup>

### 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.<sup>41</sup> 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.<sup>42</sup> Several medications used during mechanical ventilation, such as ketamine, benzodiazepines, and opioids,

have also been associated with inhibition of esophageal motor activity.<sup>41</sup>

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.<sup>43</sup> Another hypothesis describes the disproportionate activation of an inhibitory feedback pathway originating in the proximal small intestine or duodenum (“excessive feedback”).<sup>44</sup> The “excessive feedback theory” is based on the nutrient release of neuroendocrine peptides such as cholecystokinin (CCK) and 5-HT (via 5-HT<sub>3</sub> 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.<sup>45</sup>

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.<sup>5</sup> A functional ileus occurs commonly in critically ill patients.<sup>40</sup> A recent hypothesis suggests a loss of synchronized coordination and dysfunctional peristalsis as a cause of ileus in critically ill patients.<sup>28</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup>

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.<sup>49</sup> 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.<sup>50</sup>

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.<sup>51,52</sup> 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,<sup>53</sup> 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<sup>54</sup>), GI ulceration,<sup>55</sup> infectious diseases (eg, parvoviral enteritis,<sup>56,57</sup> GI parasites, and bacterial infections), postoperative abdominal surgery, gastric neoplasia (eg, lymphoma, mast cell disease), and gastric dilatation and volvulus.<sup>58</sup> Secondary defects have been identified in veterinary patients and include acute stress,<sup>59</sup> inflammation of the viscera (eg, pancreatitis, peritonitis), electrolyte derangements, metabolic disturbances (eg, acidosis, hypoadrenocorticism, hepatic encephalopathy, uremia), drugs, diabetic gastropathy,<sup>60</sup> splanchnic hypoperfusion, hypoxemia, obesity, the presence of SIRS or sepsis,<sup>61</sup> and neoplasia.<sup>62,63</sup>

A growing number of studies have been published evaluating the effects of experimental stress on GI function in animals and people.<sup>59,64</sup> 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.<sup>65,66</sup> 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.<sup>66</sup> Electrolyte disturbances have been shown to slow intestinal motility and have been demonstrated for hypokalemia,<sup>67</sup> hypermagnesemia,<sup>68</sup> and hyper- or hypocalcemia<sup>69</sup> 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<sup>70</sup> have been shown to inhibit GI transit by reducing Ach release and altering neuronal excitability.<sup>71</sup> Opioids can also increase smooth muscle activity, but they inhibit coordinated propulsive peristalsis, leading to disordered nonpropulsive contractile activity.<sup>72</sup> In many animal models, even a fraction of the analgesic dose for an opiate was enough to inhibit intestinal motility.<sup>73</sup> 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.<sup>74</sup> 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.<sup>75</sup> 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.<sup>76-78</sup>

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.<sup>79</sup> 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.<sup>80</sup> 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.<sup>80</sup> 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<sup>81</sup> and may improve immune function,<sup>82</sup> but the clinical benefit of this approach has been questioned.<sup>83</sup>

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,<sup>84</sup> VIP,<sup>85</sup> and NO<sup>86</sup> *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.<sup>87</sup>

### 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.<sup>28,88</sup> 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).<sup>48</sup> 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.<sup>89</sup> 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.<sup>90</sup> 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

**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
- 

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).

Gastroesophageal reflux and subsequent aspiration pneumonia are very common sequelae of GIDM in critically ill people, and small animal patients.<sup>37,41,42,91–93</sup> Gastroesophageal reflux occurs most commonly during and postanesthesia in small animal patients.<sup>93,94</sup> 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.<sup>95</sup> In a retrospective article evaluating aspiration pneumonia in dogs, the authors found that 23% of patients with GI dysfunction developed aspiration pneumonia.<sup>96</sup> Gastroesophageal reflux can also directly cause esophagitis, leading to complications with early EN and treatment.<sup>97</sup>

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.<sup>38,98</sup> One hypothesis, often referred to as “gut-derived sepsis,” describes bacterial translocation from the gut, promotion of septicemia, and eventual multiorgan dysfunction.<sup>99–101</sup> Several medical reports have indicated that people’s gut flora can also directly affect the ENS and motility in the gut.<sup>102,103</sup> In people with SIRS, investigators found that GIDM was associated with altered gut flora as well as with higher septic mortality.<sup>39</sup> 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.<sup>104</sup> 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.<sup>105,106</sup>

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.<sup>107</sup> 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.<sup>108</sup> 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.<sup>109</sup> Clinical signs of GIDM were evaluated in recent retrospective studies of critically ill dogs undergoing nasogastric feeding.<sup>110,111</sup> The prevalence of vomiting and regurgitation was found to be 11%<sup>110</sup> of patients in one study and 24–26%<sup>111</sup> 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.<sup>3</sup> 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.<sup>112</sup>

### 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.<sup>113</sup>

### 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,<sup>113</sup> barium mixed with food,<sup>114–116</sup> and radiopaque indigestible materials (eg, barium-impregnated polyethylene spheres).<sup>117,118</sup> 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.<sup>119</sup> 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<sup>120–123</sup> and have been validated and applied in human medicine.<sup>124</sup> 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<sup>122</sup> recently compared a <sup>13</sup>C octanoic acid (<sup>13</sup>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<sup>125–127</sup>; 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.<sup>111</sup> 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 radiosciintigraphy,<sup>128</sup> <sup>13</sup>C breath tests,<sup>129</sup> lactulose breath tests,<sup>130</sup> manometry,<sup>131,132</sup> tracer studies,<sup>133</sup> and MRI.<sup>134</sup> Imaging of the passage of a radiolabeled test meal by use of gamma camera (ie, radiosciintigraphy) is the research standard for assessing gastric emptying<sup>128</sup>; however, it is not readily available in clinical practice. The <sup>13</sup>C breath tests (eg, <sup>13</sup>C-octanoate and <sup>13</sup>C-glycine) are a noninvasive method for assessment utilized widely in human research medicine, and the effectiveness of the <sup>13</sup>C-acetate breath test has recently been validated in dogs.<sup>129</sup>

Small intestinal transit times have been evaluated with a lactulose breath hydrogen test. Researchers evaluated oro-caecal transit time in six healthy dogs with a hydrogen breath test using lactulose and the sulphasalazine/sulphapyridine method, where both techniques were validated.<sup>130</sup> 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.<sup>132,135</sup> 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.<sup>48</sup> Early EN has improved the treatment of critically ill small animal veterinary patients, and it remains an important treatment strategy.<sup>57,136–138</sup>

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.<sup>1,139–141</sup> 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.<sup>138</sup> 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.<sup>142</sup>

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.<sup>29,143</sup> 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.<sup>144–146</sup> Interestingly, the efficacy of nasojejunal feeding and post-pyloric feeding protocols have been called into question as compared to gastric feeding due to a lack of benefit found in a recent study.<sup>108</sup>

### 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.<sup>147</sup> Additionally, aggressive fluid resuscitation with subsequent intestinal edema and its detrimental effect on GI motility has also been well recognized.<sup>148,149</sup> 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.<sup>150</sup> 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 Pain management	Ambulate early Provide adequate analgesia Minimize use of opiates – consider regional analgesia and multimodal pain management	Stimulate bowel activity 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.<sup>151</sup> The cellular mechanisms by which gut edema affects intestinal transit are not completely understood, but the presence of nuclear factor kappa B<sup>152</sup> and increased expression of inducible NO synthase and subsequent NO production have been suggested.<sup>153</sup> 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.<sup>152</sup> Increased NO upregulates smooth muscle cyclic guanosine monophosphate, effectively deterring smooth muscle contractility by impeding myosin light chain phosphorylation and actin/myosin cross-linking.<sup>150</sup>

Limited volume fluid resuscitation strategies to avoid interstitial and intestinal edema have been evaluated in several recent human studies.<sup>151,154,155</sup> 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.<sup>156</sup> Hypertonic saline has been recommended and evaluated as it has been shown to alter hydraulic conductivity, decrease intestinal edema, and improve overall GI transit.<sup>149,157</sup> 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 us-

ing 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.<sup>158,159</sup> 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.<sup>160</sup> 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.<sup>161</sup> 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.<sup>162</sup> 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.<sup>163–165</sup> 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.<sup>163,166</sup> 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.<sup>167,168</sup> Nonsteroidal anti-inflammatories may also be effective in achieving multimodal analgesia with minimal effect on gut motility.<sup>169</sup> 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*,<sup>170</sup> rhubarb<sup>171</sup>), and acupuncture,<sup>172–174</sup> 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.<sup>175–177</sup> 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.<sup>178</sup> 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 sum-

marized 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<sub>2</sub>) 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.<sup>5</sup> 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.<sup>179,180</sup> 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<sub>2</sub> receptor), and metoclopramide (D<sub>2</sub> receptor).

### Domperidone

Domperidone acts as a peripheral D<sub>2</sub> antagonist and has  $\alpha_2$ - and  $\beta_2$ -adrenergic receptor antagonistic effects.<sup>53,181</sup> The prokinetic effects of dopaminergic antagonists may not be entirely explained by inhibition of dopaminergic neurons, likely owing more to the adrenergic antagonistic effects.<sup>53</sup> Domperidone seems to be less efficacious than metoclopramide as a gastric prokinetic<sup>182</sup> and may actually decrease the frequency of corporeal, pyloric, and duodenal contractions and deteriorate antropyloroduodenal coordination in the dog.<sup>183</sup> 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.<sup>184</sup> 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 <sub>2</sub> ) antagonist Serotonergic agonist (5HT <sub>4</sub> )	0.2–0.5 mg/kg PO, IV, SQ q8h CRI: 1–2 mg/kg/d IV
Domperidone Cisapride	Dopaminergic (D <sub>2</sub> ) antagonist Serotonergic agonist (5HT <sub>4</sub> ) Serotonergic antagonist (5HT <sub>1,3</sub> )	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 <sub>3</sub> )	0.5–1.0 mg/kg, IV, PO q8h–q12h
Ranitidine	Acetylcholinesterase inhibitors H <sub>2</sub> – histaminergic antagonist	1.0–2.0 mg/kg PO q8h–q12h
Nizatidine	Acetylcholinesterase inhibitors H <sub>2</sub> – 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.<sup>185</sup> The role of 5-HT in the gut is complex and involves multiple receptor subtypes (5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and 5-HT<sub>7</sub>) present in the GI tract.<sup>186</sup> Motility of the gut is mainly regulated by receptor 5-HT<sub>4</sub>. Presynaptic 5-HT<sub>4</sub> stimulates Ach release from postganglionic cholinergic neurons, resulting in smooth-muscle contraction.<sup>53,187</sup> 5-HT<sub>4</sub> 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<sub>1</sub>, 5-HT<sub>3</sub>) in motility enhancement and antiemetic effects. Antagonism of the 5-HT<sub>3</sub> 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<sub>4</sub> agonist, 5HT<sub>1</sub>, and 5HT<sub>3</sub> antagonist) and metoclopramide (5HT<sub>4</sub> agonist, 5HT<sub>3</sub> 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.<sup>188</sup> 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<sub>4</sub> agonism of the ENS.<sup>188,189</sup> Cisapride also has antagonistic effects at 5-HT<sub>1</sub> and 5-HT<sub>3</sub> receptors<sup>190</sup> of the enteric cholinergic neurons and direct agonistic effects (5-HT<sub>2α</sub>) on colonic smooth muscle.<sup>53</sup>

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 has been shown to be more potent than metoclopramide in combating delayed gastric emptying in small animal patients.<sup>191,192</sup> Cisapride is one of the few prokinetics that affects small intestinal motility by stimulating jejunal spike burst migration, jejunal propulsive motility, and antropyloroduodenal coordination.<sup>193,194</sup> Cisapride also stimulates colonic motility and can be justified as a treatment of idiopathic constipation and colonic pseudo-obstruction.<sup>195–197</sup>

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-<sub>2</sub> adrenergic agonists, dopamine, or antral tachygastria) higher doses of 0.5–1.0 mg/kg per os may be needed.<sup>53</sup> 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.<sup>198</sup> 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.<sup>199</sup> 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<sub>2</sub> receptor subtypes), serotonin 5HT<sub>4</sub> agonist, and 5HT<sub>3</sub> receptor antagonist.<sup>5,190</sup> Through its dopaminergic and 5HT<sub>3</sub> 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<sub>4</sub> agonism, and dopaminergic antagonism,<sup>5,53</sup> 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.<sup>5</sup>

Metoclopramide has been shown to potentiate lower esophageal tone, decrease fundic receptive relaxation, and increase gastric emptying in veterinary species.<sup>200</sup> 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.<sup>53</sup> Metoclopramide reestablishes antropyloroduodenal coordination in states of delayed gastric emptying.<sup>44,53,183</sup> Coordination of the upper GI tract results in accelerated gastric emptying and reduced esophageal reflux.<sup>183,201</sup> A recent study addressed the role of metoclopramide in increasing gastroesophageal sphincter tone in a group of anesthetized healthy dogs.<sup>202</sup> 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.<sup>191</sup> 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.<sup>191</sup> 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 in-

jectable bioerodible polymer for the controlled release of metoclopramide with some success.<sup>203</sup> 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.<sup>204</sup> It has also been hypothesized that metoclopramide increases circulating prolactin, inducing an analgesic effect, although this has only been evaluated in experimental models.<sup>205</sup>

The most common side effects of metoclopramide include adverse effects collectively called “extrapyramidal signs” with a reported incidence of 0.2%.<sup>206</sup> In high-risk human patients, the risk of these side effect can increase up to as high as 25%.<sup>206</sup> 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).<sup>207</sup>

## Novel serotonin agonists

Novel serotonin agonists that are currently under investigation in human and animal studies include velusetrag (TD-5108),<sup>208</sup> tegaserod,<sup>209</sup> mosapride,<sup>210,211</sup> and prucalopride.<sup>212–214</sup> Mosapride is a novel 5-HT<sub>4</sub> receptor agonist that enhances GI motility. It is used as a prokinetic in people and has recently been evaluated for use in dogs.<sup>210,215</sup> Tegaserod, a potent partial 5-HT<sub>4</sub> agonist and a weak 5-HT<sub>1D</sub> receptor agonist, has been shown to increase antral, duodenal, jejunal, and colonic motility in conscious dogs.<sup>216,217</sup> Studies by Nguyen *et al*<sup>218</sup> using varying doses of tegaserod in dogs showed acceleration in colonic transit, although the effects on upper GI transit were more variable.<sup>209,217</sup> Tegaserod has been investigated for postoperative ileus in horses<sup>219,220</sup>; 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.<sup>221</sup> 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.<sup>222,223</sup> 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.<sup>224,225</sup> 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.<sup>226</sup> 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.<sup>227</sup> 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<sub>3</sub> cholinergic pathways, whereas in cats the effect occurs via direct stimulation of smooth muscle motilin receptors.<sup>53</sup> In many species, erythromycin has been shown to lower LES tone, increase antral contractions and gastric emptying, and decrease small intestinal transit time.<sup>228</sup> Studies in critically ill human patients demonstrate improved gastric motility and decreased GRVs in patients treated with low-dose erythromycin.<sup>229–231</sup> In a population of mechanically ventilated human patients, erythromycin decreased the time to tolerated early EN.<sup>232</sup> 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.<sup>229</sup> 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.<sup>233,234</sup> 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.<sup>5,235,236</sup> 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,<sup>237</sup> nausea, and inappetence.

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.<sup>238,239</sup> 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.<sup>240</sup> 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,<sup>241</sup> CGRP 8-37,<sup>241</sup> and GS-611.<sup>242</sup>

### 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<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub>.<sup>243–245</sup> Species variability exists with location, tissue type, and prevalence of receptor subtypes.<sup>246</sup> All histamine receptors are present in the GI tract, but their predominant action and influence vary. Histamine H<sub>1</sub> receptor activation causes contraction similar to that of muscarinic receptor activation by increasing calcium availability.<sup>247</sup> Histamine H<sub>2</sub> receptors can mediate neurogenic contractions by facilitating both cholinergic and noncholinergic excitatory transmission.<sup>246,248</sup> H<sub>2</sub> receptor antagonists are used widely for the treatment of gastric acid related disease in dogs and cats, while agents ranitidine and nizatidine are utilized for their prokinetic effect via acetylcholinesterase inhibition. The novel third histamine receptor type, histamine H<sub>3</sub> receptor, has been recently identified and localized throughout the GI tract,<sup>243</sup> however experimentally it has been shown to play a very minor role in regulation of GI motility. Histamine H<sub>3</sub> 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.<sup>245,247</sup>

### Ranitidine/nizatidine

Ranitidine and nizatidine are histaminergic receptor (H<sub>2</sub>) 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.<sup>249</sup> 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.<sup>5</sup> 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.<sup>72,250</sup> 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.<sup>251,252</sup>

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<sup>253,254</sup> and alvimopan.<sup>255</sup> Naloxone has been shown to increase gastric emptying in people.<sup>256</sup> 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, quaternary 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.<sup>257,258</sup> 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.<sup>259</sup> Methylnaltrexone demonstrated efficacy in 2 double-blind trials and is used in opioid-induced

constipation.<sup>73</sup> Other novel opiate antagonists, including NKTR-118,<sup>260</sup> TD-1211,<sup>261</sup> ADL-7445, and ADL-5945, are currently being investigated and have shown significant promise as a new approach to GIDM.<sup>262–264</sup>

### 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,<sup>265,266</sup> CCK receptor antagonists,<sup>267–269</sup> guanylate cyclase 2C agonists,<sup>270,271</sup> and ileal bile acid transporter antagonists.<sup>272,273</sup> Lubiprostone, a type-2 chloride channel (ClC-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.<sup>265</sup> 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.<sup>45,267,268</sup> 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.<sup>271</sup> 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.<sup>272</sup>

### Prognosis

An increase in morbidity and mortality has been seen in critically ill people with evidence of GIDM compared to patients without.<sup>37,41,42,91–93</sup> 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.

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