Prevalence and Risk Factors for Development of Hemorrhagic Gastro-Intestinal Disease in Veterinary Intensive Care Units in the United Kingdom

Abstract

Objective: To determine the prevalence of hemorrhagic gastro-intestinal (GI) disease developing in dogs and cats admitted for management of non-GI disease in veterinary intensive care units (ICUs).

Design: Retrospective study of animals presented between October 2012 and July 2013.

Setting: Three ICUs located in veterinary teaching hospitals in the United Kingdom.

Animals: Dogs (n=272) and cats (n=94) were consecutively enrolled from three ICUs if they were hospitalized in the unit for at least twenty-four hours. Cases were excluded if they had hemorrhagic GI disease in the forty-eight hour period before presentation or in the twenty-four hour period after admission. Cases were also excluded if they suffered skull fracture, epistaxis or hemoptysis, if they underwent surgical procedures of the GI or upper respiratory tracts, or if they were presented for management of GI disease.

Measurements and Main Results: Hemorhagic GI disease was observed in dogs at all three units, but at different rates (Center 1: 10.3%, Center 2: 4.8%, Center 3: 2.2%). Hemorrhagic GI disease was not observed in cats at any of the participating centers. Construction of a multivariable logistic regression model revealed that serum albumin concentration, administration of prophylactic gastro-protectant drugs and institution were significantly associated with the development of hemorrhagic GI disease in dogs. Development of hemorrhagic GI disease and placement of a feeding tube were significantly associated with mortality during the period of hospitalization in dogs. Thirty-seven (13.6%) dogs and 12 (12.8%) cats died or were euthanized while hospitalized, with a higher mortality rate (42.1%) in dogs with hemorrhagic GI disease.

Conclusions: Hemorrhagic GI disease does develop in dogs hospitalized for management of non-GI disease, but this phenomenon was not observed in cats. Development of hemorrhagic GI disease appeared to have a significant impact on survival in veterinary ICUs.

Keywords: Stress-related mucosal disease, stress ulcer prophylaxis, omeprazole, enteral feeding

Abbreviations: GI: gastro-intestinal; GMB: gastric mucosal barrier; ICU: intensive care unit; MODS: multiple organ dysfunction syndrome; NSAID: non-steroidal anti-inflammatory drug; ROC: receiver operator characteristic; SIRS: systemic inflammatory response syndrome; SRMD: stress-related mucosal disease

Introduction

In human medicine, stress-related mucosal disease (SRMD) refers to the development of erosive lesions of the stomach and intestines in patients admitted to ICUs for management of severe illness[1]. The term covers a spectrum of disease, from superficial mucosal injury detectable only by gastroduodenoscopy to severe ulceration that results in clinically important hemorrhage. Overt clinical bleeding due to SRMD was reported to occur in approximately 4% of humans admitted to a group of ICUs in Canada[2], and development of this disease significantly increased the risk of death during the period of hospitalization.

Impaired perfusion of the gastric mucosal barrier (GMB) is the proximate cause of SRMD, but development of the disease is reflective of systemic changes in hemodynamic status and inflammatory cascade[3]. Splanchnic hypoperfusion caused by sympathetic stimulation or hypovolemia is likely to be an important factor in the development of SRMD but it may be difficult to detect in patients that appear to

have adequate macrohemodynamic markers of systemic perfusion[4]. Reduced splanchnic blood flow also increases the risk of reperfusion injury caused by oxygen free radicals if blood flow is restored after appropriate resuscitation[5]. Local or systemic production of pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukins 1 and 8 causes further alterations in perfusion of the gastric mucosa and disrupts the production of mucus and bicarbonate[6], which are required for neutralization of gastric acid. If the GMB is sufficiently disrupted by these changes, gastric acid may cause direct damage to the mucosa, and this process can progress to cause substantial ulceration and hemorrhage.

Several factors have been identified in human patients that increase the risk of development of SRMD[2], particularly respiratory failure necessitating mechanical ventilation and coagulopathy. Administration of prophylactic gastro-protectant medications reduces the risk of SRMD[2], but this may be associated with development of other complications, such as aspiration pneumonia, because increased gastric pH permits bacterial colonization of the stomach[13].

Hemorrhagic GI disease has not been described specifically in veterinary ICUs, but two studies identified subclinical gastric erosions in dogs that underwent decompressive surgery for intervertebral disc disease, some of which also received glucocorticoids[7,8]. These lesions did not appear to be responsive to administration of gastro-protectant medications. The pathogenesis of gastric ulceration in Alaskan sled dogs at the Iditarod race may also share some features with that of SRMD in people. Strenuous exercise in these dogs resulted in increased gastric permeability and increased frequency of gastric lesions observed by endoscopy[9,10]. The authors of this study speculated that these changes could occur due to increased circulating glucocorticoid concentrations or diversion of cardiac output to skeletal muscle for exercise. Two further studies described development of gastroduodenal ulceration in critically ill animals in association with various underlying causes, including hepatic disease, pancreatitis, hypoadrenocorticism, and administration of non-steroidal anti-inflammatory drugs (NSAIDs)[11,12].

The primary aim of this study was to determine the proportion of animals that developed overt hemorrhagic GI disease in veterinary ICU patients. It was hypothesized that this would occur at similar rates to those reported in human ICUs, and that dogs would develop the disease more frequently than cats based on previous evidence suggesting that the GI tract is not the shock organ of cats. Secondary aims were to investigate risk factors for the development of hemorrhagic GI disease, and to determine whether development of these signs was associated with mortality during the period of hospitalization.

Materials and Method

Study design A retrospective multi-center survey was conducted at three intensive care units (Centers 1, 2 and 3) located in teaching hospitals in the UK. These units accept referral cases from veterinarians in general practice and from other specialist services within the same institutions. Case management in each unit is supervised by board certified clinicians in emergency and critical care, internal medicine, surgery or neurology. Entry and egress of patients from the ICUs and use of any drugs, including gastro-protectant medications, were at the discretion of the attending clinician.

All cases presenting consecutively to the ICUs were considered eligible for enrolment during the period of the study if they were hospitalized for at least twenty-four hours. Cases were excluded if they had a history of hemorrhagic GI disease in the forty-eight hours prior to hospitalization or if they developed signs within the first twenty-four hours after admission. Cases were also excluded if they underwent surgical procedures involving the GI or upper respiratory tracts, if they presented with or developed epistaxis or hemoptysis, if they presented for management of GI disease, or if they had sustained one or more skull fractures. Cases were not excluded if they received gastro-protectant drugs, NSAIDs, glucocorticoids or anticoagulants prior to admission or during hospitalization, nor if they were diagnosed with diseases that may cause secondary GI signs, such as hypoadrenocorticism.

Data collection: A single entry form was produced for each case enrolled in the study (Supplementary Data 1), and this was completed by a veterinarian after the patient was discharged from the ICU. The veterinarian completing the enrolment form did not necessarily have primary responsibility for the case. The following data were collected from the medical records of each case: signalment, presenting problem and problems identified after initial consultation, concurrent diseases and medications, clinical examination findings, GI signs observed while hospitalized, and results of complete blood cell count, serum biochemistry and coagulation profiles performed on admission. Types of feeding tube placed in individual patients were recorded, as were the types and doses of any gastro-protectant, NSAID, glucocorticoid or antithrombotic medications administered in the ICU. The length of hospitalization, the nature of any surgical procedures conducted immediately before or during the period of ICU hospitalization, and mortality or euthanasia while hospitalized were also noted.

SRMD was defined as hemorrhagic GI disease manifesting as hematemesis, melena or hematochezia or as mucosal erosions and hemorrhage observed during GI endoscopy. Dogs were diagnosed with systemic inflammatory response syndrome (SIRS) if they fulfilled two or more of the following four conditions: rectal temperature <37.2C or >39.2C, heart rate >140 beats per minute, respiratory rate >30 breaths per minute, or total white blood cell count $<6x10^9$/l (6,000/µl) or $>19x10^9$/l (19,000/µl)[15].

Statistical analysis: All statistical analyses were conducted using a commercial software program[a]. Shapiro-Wilks tests and visual assessments of histograms were used to determine whether variables were parametrically distributed. Parametric and non-parametric variables were compared using Student's *t* tests and Mann-Whitney *U* tests, respectively. Categorical data were compared using Fisher's exact tests or Chi squared tests. Confidence intervals, where stated, are at the 95% level.

The proportion of veterinary patients that developed SRMD was determined by dividing the number of cases with hematemesis, melena or hematochezia by the total number of included cases collectively and for each ICU, and 95% confidence intervals were calculated.

Multivariable logistic regression was used to evaluate risk factors for development of SRMD and for mortality during hospitalization. Univariable analyses were first conducted using Mann-Whitney *U* tests, Chi squared tests or Fisher's exact tests, and variables with *p* values <0.2 were retained. These variables were entered together in the multivariable analysis, and a model was fitted using a forward entry method based on calculation of likelihood ratios. A categorical variable describing whether prophylactic gastro-protectant medications were administered was forced into the final model for development of SRMD, and a variable describing whether cases fulfilled the SIRS criteria was forced into the model of mortality as these factors were considered to be of considerable *a priori* importance for each model based on published evidence[2,16]. Institute was included as a factor in both models to account for possible differences between centers. Hosmer-Lemeshow tests were performed to assess the adequacy of model fit, and receiver operator characteristic (ROC) curves were produced using probabilities derived from each logistic regression model to determine the predictive capability of each model.

Results

Study populations: After removal of duplicate cases and application of exclusion criteria, 272 dogs and 94 cats were included in the study (Figure 1). Of the dogs included, 159 (58.5%) were from Center 1, 21 (7.7%) were from Center 2, and 92 (33.8%) were from Center 3. Of the cats, 67 (71.3%) were from Center 1, 7 (7.4%) were from Center 2, and 20 (21.3%) were from Center 3. Seventy-one dogs were intact males, 37 intact females, 82 neutered males and 82 neutered females, whereas 3 cats were intact males, 4 intact females, 51 neutered males and 36 neutered females.

There was no difference in median age between dogs and cats, nor between animals of either species at different centers.

Prevalence of GI disease: The proportion of dogs that developed SRMD was 10.3% (CI: 6.3-15.7) at Center 1, 4.8% (CI: 0.85-22.7) at Center 2 and 2.2% (CI: 0.6-7.7) at Center 3, with a combined proportion of 7.0% (CI: 4.5-10.7). The difference in proportions between centers was not significant (Chi square 5.2, p=0.075). SRMD did not occur in any of the cats observed during this study at any center. Among the dogs that received prophylactic gastro-protectant medications, the proportion that developed SRMD was 16.4% (CI: 8.9-28.3), compared to 4.2% (CI: 2.2-7.8) in dogs that did not receive prophylaxis, and there was a significant difference in these proportions (Chi square 10.3, p=0.001). Rates of development of SRMD during hospitalization in dogs and cats at each center are shown in Table 2.

Of the dogs that developed SRMD (n=19), the most common diagnoses were immune-mediated disease (4), neoplasia (2), trauma (2), and *Angiostrongylus vasorum* infestation (2). The remaining dogs were diagnosed with pyelonephritis (1), fasciitis (1), traumatic brain injury (1), hepatic disease (1), intervertebral disc protrusion (1), hypoadrenocorticism (1), sudden acute retinal degeneration syndrome (1), sepsis and disseminated intravascular coagulation (1), and intra-abdominal hemorrhage following ovariohysterectomy (1).

Feeding tubes were placed in 27 animals across all centers. Only esophagostomy tubes were placed in cats (n=7), but naso-esophageal (n=12), esophagostomy (n=5) and gastrostomy (n=3) tubes were placed in dogs. The majority of the tubes were placed at Center 1 (n=23), with a smaller number at Center 3 (n=4). Placement of a feeding tube was undertaken at Center 1 after a median period of anorexia of 3 days (IQR: 3-5, range 2-9, n=13). The duration of anorexia could not be determined in 6 dogs, and a

naso-esophageal feeding tube was placed in the remaining 4 dogs as a standard preparation for mechanical ventilation.

Evaluation of risk factors for development of SRMD: Univariable analyses revealed that multiple factors were associated with development of SRMD (Table 3). When these variables were entered into the multivariable analysis, decreased serum albumin concentration, institute and administration of prophylactic gastro-protectant medications were retained in the final model. Dogs with SRMD were 4.3 (CI: 1.2-15.5) times more likely to have decreased serum concentrations of albumin, 4.3 (CI: 1.4-13.7) times more likely to have received prophylactic gastro-protectant medications and 10.0 (CI: 1.7-33.3) times less likely to have been hospitalized at Center 3 than those that did not develop SRMD. Performance of the Hosmer-Lemeshow test indicated good model fit (Chi Square 2.2, p=0.826), and the area under the ROC curve constructed using model probabilities was 0.79 (CI: 0.68-0.90)(Supplementary Figure 1A), showing that the model was able to discriminate adequately between cases with and without SRMD. A ROC curve was also generated using individual values for serum albumin concentration (n=201), and the area under the curve was smaller using this model (0.68, CI: 0.52-0.84)(Supplementary Figure 1B). Using a cut-off value of 28.0 g/l (2.8 g/dl), the sensitivity and specificity values for prediction of development of SRMD were 0.67 and 0.62, respectively.

Hospitalization and survival: The median durations of hospitalization and mortality rates for dogs and cats at different centers are shown in Table 2. There was no difference in duration of hospitalization between cats and dogs from all centers, but average length of hospitalization was greater at both Centers 2 (p=0.048) and 3 (p<0.001) compared to Center 1. Thirty-seven (13.6%) dogs and 12 (12.8%) cats died or were euthanized while hospitalized. Mortality rates were similar between centers and species, but the proportion of dogs with SRMD that did not survive to discharge (8/19 dogs, 42.1%)

198 was significantly greater than for dogs that did not develop SRMD (29/252, 11.5%; Chi square 14.0,
199 $p<0.001$).
200
201 ***Evaluation of risk factors for mortality during hospitalization***: Significant associations were
202 detected between several variables and mortality during hospitalization using univariable analysis (Table
203 4). When these variables were entered into the multivariable analysis, placement of a feeding tube and
204 development of SRMD were associated with mortality. Dogs that died or were euthanized while
205 hospitalized were 13.3 (CI: 4.0-43.5) times more likely to have had a feeding tube placed and 5.1 (CI:
206 1.6-15.9) times more likely to have developed SRMD than those that were discharged. Fulfilment of the
207 SIRS criteria and institute were forced into the final model, but these variables were not significantly
208 associated with mortality. The model fit was adequate (Hosmer-Lemeshow Chi square 5.7, $p=0.338$), and
209 generation of a ROC curve using model probabilities yielded an area under the curve of 0.77 (CI: 0.68-
210 0.86)(Supplementary Figure 2).
211
212 Naso-esophageal feeding tubes were placed routinely in dogs that were mechanically ventilated.
213 When these animals were excluded from the analysis (n=4), the odds ratio for tube placement decreased
214 to 8.5 (CI: 2.4 – 30.3, $p=0.001$), while that for development of SRMD did not change considerably (OR:
215 5.1, CI: 1.6 – 15.9, $p=0.006$). Model fit parameters were similar to those reported above (data not
216 shown).
217

218 ## Discussion

219 The results of this study show that hemorrhagic GI disease, defined here as SRMD, does occur in
220 dogs hospitalized in veterinary ICUs, but was not observed in any of the cats that were included. Dogs
221 with SRMD were more likely to have decreased serum concentrations of albumin on presentation, but this
222 parameter had a low sensitivity and specificity for prediction of development of this disease. Affected

223 animals were also more likely to have received prophylactic gastro-protectant medications and less likely
224 to have been hospitalized at Center 3. SRMD and placement of a feeding tube were significantly more
225 likely to occur in dogs that died or were euthanized while hospitalized.
226
227 The proportion of dogs that developed SRMD varied considerably between Centers, and dogs at
228 Center 3 were at significantly reduced risk compared to either Center 1 or 2. The cause of this difference
229 is not apparent: SRMD could have developed at similar rates at Centers 2 and 3 as at Center 1 but was not
230 recorded, although the authors consider this scenario to be unlikely as occurrence of all forms of GI
231 disease is considered to be a notable event among nursing staff and attending clinicians at all three
232 centers. The true prevalence of SRMD at Center 2 may also differ from that reported due to the small
233 number of cases observed in this study, as indicated by the wide confidence intervals for this parameter.
234
235 Measurable hemorrhage due to stress-related GI injury is reported to occur in approximately 4-
236 6% of affected humans[2,16], which is broadly comparable to the proportion of dogs affected with SRMD
237 defined according to this study. In contrast to human intensive care, none of the animals included in this
238 study underwent gastroduodenoscopy, which is a much more sensitive technique for detection of
239 superficial erosions in the acid-secreting sections of the stomach. When this technique was applied in
240 dogs undergoing surgery for management of inter-vertebral disc disease, subclinical lesions were
241 observed in approximately 75% of patients[7,8]. The animals considered in this study are therefore likely to
242 represent the most severely affected patients in a spectrum of stress-related GI disease, similar to the
243 syndrome of clinically important bleeding in humans with SRMD.
244
245 SRMD was not observed in any of the 94 cats that were included in this study, and this finding is
246 consistent with the hypothesis that the GI tract is not a 'stress organ' in cats. Previous experimental[17] and
247 epidemiologic[18,19] studies indicate that cats are susceptible to pulmonary injury when suffering from

systemic inflammation or sepsis, and there are no previous reports suggestive of SRMD in this species. Observation of a greater number of cats in ICUs is likely to be required to determine whether SRMD occurs at lower prevalence than could be detected during this study.

Dogs that developed SRMD were more likely to have decreased serum albumin concentrations at presentation. Albumin is an essential product used in maintaining the GMB, and dogs with decreased albumin concentrations are reported to be at increased risk of dehiscence following incisional biopsy of the small intestine[20]. It is therefore possible that dogs with hypoalbuminemia are at increased risk of SRMD and other GI signs due to their inability to maintain an effective mucosal wall. Alternatively, the albumin concentration could be decreased in patients that have clinically undetectable GI injury resulting in increased GI permeability and protein-losing enteropathy, prior to the onset or recognition of hemorrhagic GI disease. Investigation of Alaskan sled dogs indicated that increased gastric permeability was an early event in development of erosive gastric disease in this cohort[10], suggesting that hypoalbuminemia could be an effect rather than a cause of the GI signs observed. Hypoalbuminemia in this study may also represent a non-specific marker of illness, as serum albumin is a negative acute phase protein. Decreased serum concentrations of albumin have also been identified as negative independent prognostic factors in two studies of dogs admitted to veterinary ICUs[21,22].

With a cut off value of 28.0 g/l (2.8 g/dl, the lower limit of the reference range in use at Center 1), serum albumin concentration had a poor sensitivity and specificity for prediction of the development of SRMD, limiting the usefulness of this parameter in guiding the use of prophylactic interventions. Further studies will be required to establish whether patients with hypoalbuminemia would benefit from administration of gastro-protectant medications.

Gastro-protectant medications were administered to a large proportion of the animals included in this study, which complicated the interpretation of the results obtained, particularly because animals that ultimately developed SRMD were more likely to have received one or more of these products. This variable was included when fitting the logistic regression model due to its *a priori* importance[2], but it would have been preferable to evaluate groups of treated and untreated dogs separately in a stratified model[23]. This approach was not attempted in this study as the number of cases in each subgroup would have been insufficient to evaluate the number of risk factors included.

Univariable analysis identified several other factors that were significantly associated with development of SRMD, including several that have previously been associated with the analogous disease in humans, such as hepatopathy, nephropathy and thrombocytopenia. Cook and colleagues[2] reported hepatic and renal failure as significant risk factors for development of clinically important bleeding after univariable analysis, but only secondary coagulopathy and respiratory failure necessitating mechanical ventilation were retained in the multivariable model. Failure to identify these variables as risk factors for SRMD in this study probably relates to the relatively low prevalence of these problems in this sample, and in veterinary ICU caseloads in the UK.

SRMD and placement of a feeding tube were significantly more likely to occur in dogs that died or were euthanized compared to those that were discharged. Placement of a feeding tube is considered to be a relatively benign procedure[24] and, in this group of patients, was usually performed at the same time as imaging or other procedures that necessitated general anesthesia or sedation. Placement of a feeding tube in this model is more likely to be a proxy variable that could represent a prolonged history of anorexia or anticipated anorexia, or a patient likely to require a long period of intensive care following placement. Feeding tubes were also placed in four patients in preparation for mechanical ventilation, which is also likely to be a poor prognostic indicator in veterinary ICU patients[25]. The authors do not

297 consider that use of a feeding tube *per se* should increase the risk of death as this procedure is usually
298 well tolerated or is associated with only minor complications[24]. Procedures are also employed at all three
299 centers to minimize the risk of refeeding syndrome in dogs with prolonged anorexia.
300
301 Evidence from human medicine suggests that enteral nutrition should be beneficial for patients
302 with stress-related GI disease[26], and early re-introduction of enteral feeding may reduce the requirement
303 for gastro-protectant medications. A recent pilot study of dogs with pancreatitis further indicated that
304 enteral feeding was well tolerated in critical care patients and was not associated with a greater prevalence
305 of adverse effects compared to administration of parenteral nutrition[27], and a study of dogs with septic
306 peritonitis suggested that introduction of early enteral nutrition was associated with shorter duration of
307 hospitalization[28]. Nevertheless, it remains to be determined in future studies whether re-introduction of
308 enteral nutrition would prevent the hemorrhagic GI disease reported in patients in this study.
309
310 Development of hemorrhagic GI disease in patients that did not present for investigation or
311 management of GI disease is likely to cause increased morbidity, either due to development of anemia,
312 production and release of further inflammatory mediators, or increased risk of bacterial translocation
313 across the wall of the stomach or upper small intestine. SRMD may itself act as a proxy variable for
314 severe systemic disease, such as SIRS, sepsis, or multiple organ dysfunction syndrome (MODS). A
315 variable describing fulfilment of established SIRS criteria was included in the final model of factors
316 associated with mortality during hospitalization to try to account for this possibility as this factor was
317 shown to be significant in a previous study[15]. Despite this, development of SRMD remained an
318 independent predictor of mortality, and the higher risk of mortality among patients that developed SRMD
319 is consistent with findings in humans with overt clinical hemorrhage due to GI disease[2].
320

Limitations: Limitations of this study include the relatively small number of cases included, especially for investigation of risk factors for development of SRMD and mortality. Animals with SRMD were more likely to have been hospitalized at Centers 1 and 2 than Center 3, and, although institution was included as an independent factor in all multivariable analyses, it is possible that unmeasured differences between centers could have acted as confounding or modifying factors.

Although much of the data included in this study was collected prospectively, some information regarding development of GI disease was collected retrospectively from clinical records, reducing the reliability and consistency of these findings. Data were also collected by a number of different investigators who may not have been involved in the primary care of the case.

Conclusions: SRMD was observed in dogs from three different veterinary ICUs but was not observed in cats. Decreased serum albumin concentration was associated with development of SRMD, but, using a clinically relevant cut off value, this variable had a poor sensitivity and specificity for prediction of the disease. Development of SRMD and placement of a feeding tube were independently associated with increased mortality while hospitalized, but further studies will be required to determine the effects and potential benefits of prophylactic gastro-protectant therapy in veterinary ICU patients.

Footnotes

[a] IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

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Figure 1: Flow diagram of cases included in study

Supplementary Figure 1: Receiver operator characteristic curves generated using (A) probabilities from the multivariable regression model of risk factors for development of SRMD and (B) serum concentrations of albumin

Supplementary Figure 2: Receiver operator characteristic curve generated using probabilities derived from multivariable logistic regression model of risk factors for mortality during hospitalization

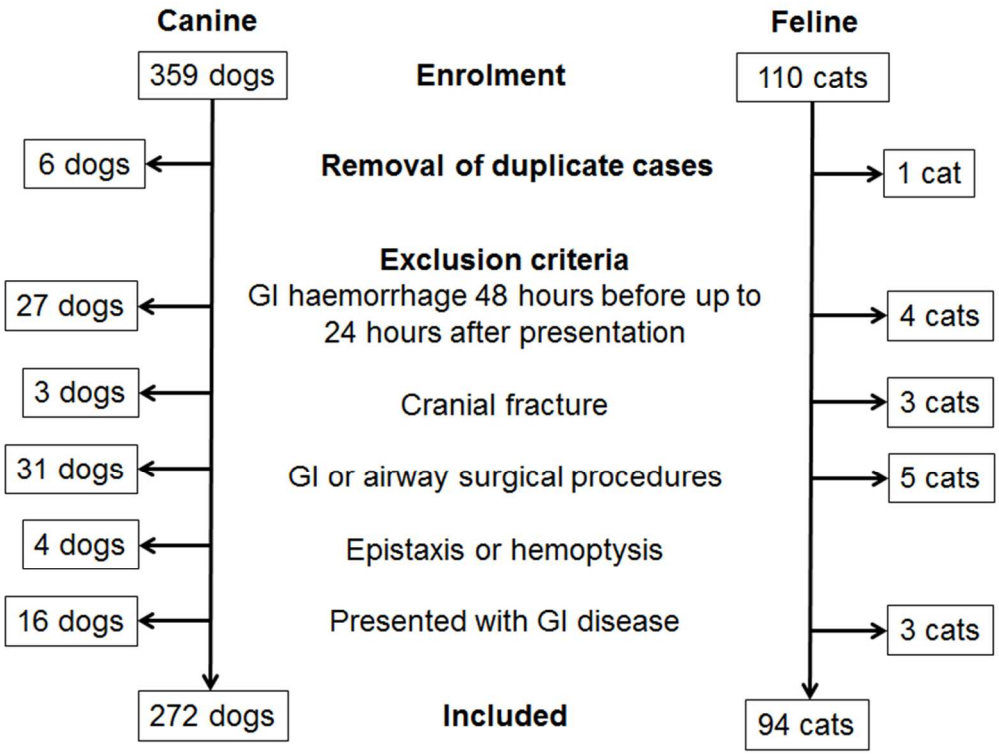
Canine
Feline
359 dogs
Enrolment
110 cats
6 dogs
Removal of duplicate cases
1 cat
Exclusion criteria
27 dogs
GI haemorrhage 48 hours before up to 24 hours after presentation
4 cats
3 dogs
Cranial fracture
3 cats
31 dogs
GI or airway surgical procedures
5 cats
4 dogs
Epistaxis or hemoptysis
16 dogs
Presented with GI disease
3 cats
272 dogs
Included
94 cats

Table 1: Summary of demographic data obtained from included patients

		Center 1		Center 2		Center 3		Combined	
		Canine	Feline	Canine	Feline	Canine	Feline	Canine	Feline
N		159	67	21	7	92	20	272	94
Time period		October 2012 to July 2013		September to November 2012		January 2013 to April 2013			
Age (years)	Median	5.9	6.9	4.8	5.0	5.0	8.5	5.1	7.2
	Inter-quartile range	2.6 – 9.4	2.3 – 12.3	2.8 – 6.0	0.8 – 10.0	3.0 – 8.0	4.0 – 12.0	2.8 – 9.0	2.9 – 12.0

*Inter-quartile range

Table 2: Summary of clinical and gastro-intestinal disease data obtained from cases

		Canine				Feline			
		Center 1	Center 2	Center 3	Combined	Center 1	Center 2	Center 3	Combined
N		159	21	92	272	67	7	20	94
SRMD* (%)		16 (10.3)	1 (4.8)	2 (2.2)	19 (7.0)	0	0	0	0
	Melena or hematochezia (%)	15 (9.4)	1 (4.8)	2 (2.2)	18 (6.6)				
	Hematemesis (%)	1 (0.6)	0	0	1 (0.4)				
	Hemorrhage observed on endoscopy (%)	0	0	0	0				
	Died/euthanized while hospitalized (% of SRMD cases)	7 (43.8)	0	1 (50.0)	8 (42.1)				
Duration of hospitalization (days)	Median	3.0	4.0	2.0	3.0	2.0	4.0	6.0	3.0

	Inter-quartile range	2.0 – 4.0	2.0 – 7.5	4.0 – 6.0	2.0 – 5.0	2.0 – 4.0	1.0 – 8.0	2.25 – 8.75	2.0 – 5.25
Died/euthanized while hospitalized (%)		27 (17.0)	1 (4.8)	9 (9.8)	37 (13.6)	4 (6.0)	1 (14.3)	7 (35.0)	12 (12.8)
Received GI§ prophylaxis (%)		28 (17.6)	9 (42.9)	19 (20.7)	56 (20.6)	1 (1.5)	3 (42.9)	1 (5.0)	5 (5.3)
	Subsequently developed SRMD* (% of those receiving prophylaxis)	6 (21.4)	1 (11.1)	2 (10.5)	9 (16.1)	0	0	0	0

*SRMD: Stress-related mucosal disease, §GI: gastro-intestinal

Table 3: Results of univariable and multivariable analysis of risk factors for development of SRMD

		Univariable factors			Multivariable model**		
		Developed SRMD¶ (%)	Did not develop SRMD¶ (%)	*p* value	Odds ratio	95% Confidence interval	*p* value
Median age (years)(interquartile range)		8.0 (5.0 – 11.3)	5.0 (2.6 – 8.5)	0.007 (Mann-Whitney *U* test)			
Institute	Center 1	16 (5.9)	143 (52.8)	0.059	1.0		
	Center 2	1 (0.4)	20 (7.4)		0.3	0.03 – 2.8	0.304
	Center 3	2 (0.7)	89 (32.8)		0.1	0.03 – 0.6	0.012
Packed cell volume	< 35%	12 (4.4)	72 (26.6)	0.003			
	≥ 35%	7 (2.6)	180 (66.4)				
Platelet count	< lower RL§	6 (3.0)	30 (15.0)	0.045			
	≥ lower RL	10 (5.0)	154 (77.0)				
Serum albumin concentration	< lower RL	11 (5.5)	94 (46.8)	0.110	4.3	1.2 – 15.5	0.026

	≥ lower RL	4 (2.0)	92 (45.8)				
Serum ALT* activity	≤ 4 x upper RL	11 (5.7)	168 (86.6)	0.019			
	> 4 x upper RL	4 (2.1)	11 (5.7)				
Serum creatinine concentration	≤ 2 x upper RL	15 (6.8)	194 (88.6)	0.176			
	> 2 x upper RL	2 (0.9)	8 (3.7)				
SIRS[Π]	No	5 (2.7)	85 (45.2)	0.086			
	Yes	13 (6.9)	85 (45.2)				
Prophylactic administration of gastro-protectant drugs	No	10 (3.7)	206 (76.0)	0.002	4.3	1.4 – 13.7	0.013
	Yes	9 (3.3)	46 (17.0)				

*ALT: alanine aminotransferase, [§]RL: reference limit, [Π]SIRS: systemic inflammatory response syndrome, [¶]SRMD: stress-related mucosal disease. **n=201.

Table 4: Results of univariable and multivariable analysis of risk factors for death while hospitalized

		Univariable factors			Multivariable model¶		
		Died (%)	Survived (%)	*p* value	Odds ratio	95% confidence interval	*p* value
Median age (years)(interquartile range)		7.5 (4.0 – 10.5)	5.0 (2.6 – 8.4)	0.037 (Mann-Whitney *U* test)			
Institute	Center 1	27 (9.9)	132 (48.5)	0.130	1.0		
	Center 2	1 (0.4)	20 (7.4)		1.3	0.2-11.3	0.808
	Center 3	9 (3.3)	83 (30.5)		0.9	0.3-2.8	0.836
Packed cell volume	< 35%	18 (6.6)	66 (24.3)	0.012			
	≥ 35%	19 (7.0)	169 (62.1)				
Platelet count	< lower RL*	8 (4.0)	28 (13.9)	0.187			
	≥ lower RL	21 (10.4)	144 (71.6)				
Serum creatinine concentration	≤ 2 x upper RL	26 (11.8)	184 (83.6)	0.006			
	> 2 x upper RL	5	5 (2.3)				

		(2.3)					
SIRS[§]	No	8 (4.2)	82 (43.4)	0.016	2.0	0.8-5.2	0.164
	Yes	22 (11.6)	77 (40.7)				
SRMD[Π]	No	29 (10.7)	223 (82.3)	0.001	5.1	1.6-15.9	0.006
	Yes	8 (3.0)	11 (4.1)				
Placement of feeding tube	None	26 (9.6)	226 (83.1)	<0.001	13.3	4.0-43.5	<0.001
	Naso-esophageal	7 (2.6)	5 (1.8)				
	Esophagostomy	2 (0.7)	3 (1.1)				
	Gastrostomy	2 (0.7)	1 (0.4)				
Mechanically ventilated	No	34 (12.5)	233 (85.7)	0.019			
	Yes	3 (1.1)	2 (0.7)				

*RL: reference limit, [§]SIRS: systemic inflammatory response syndrome, [Π]SRMD: stress-related mucosal disease. [¶]n=188.