

SMALL ANIMAL GI DISEASE

AN INTERNAL MEDICINE PERSPECTIVE

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SBCV 2020 Spring CE Series

ROUGH PLAN FOR THE DAY

- Vomiting
 - Localization, disease, diagnostics and treatments
- Diarrhea
 - Localization, disease, diagnostics and treatments
- Specific disorders that don't neatly fit into the above categories
- Case Illustrations
- I will stop for questions at the end of each major section

THE IM PERSPECTIVE

- What do we do?
 - Chronic disease
- How we can help?
 - Guide early testing/therapy
 - Deeper investigation into chronic cases/non-responders
- Need to work with together to completely treat a patient!
 - Initial diagnostics, follow up, medications, diets
 - Client relationships
 - Clients trust you immensely!

Our goal is to find an answer, make a plan, and follow it through (together)

COMMUNICATION

- Referral letters
 - Contents
 - Brief recap (you know why you sent them)
 - Relevant findings in provided diagnostic results
 - Relevant PE findings
 - My diagnostic testing
 - Pending and results if we have them
 - Diagnosis
 - Treatment plan
 - Follow up plan
- Client Communication
 - What should they know?
 - Additional testing
 - Costs
 - Time...
 - “Hail Mary” appointments?
 - Sometimes this is all that is left
 - But it doesn’t mean there are always options!

VOMITING

ALL VOMITING IS NOT CREATED EQUAL

ACUTE VOMITING

- Self-limiting vs Life Threatening
 - Life threatening gets you to the ER!
- Routine empirical measures appropriate
 - Brief fasting period
 - Bland diet
 - Empirical deworming

CHRONIC VOMITING

- This is where IM specialists can help
- Means its time to start running tests!
 - Usually after routine empiric measures have failed
 - Clients are usually more motivated to find an answer
 - Makes risks of testing more reasonable

CHRONIC VOMITING DDX

GASTROINTESTINAL ORIGIN

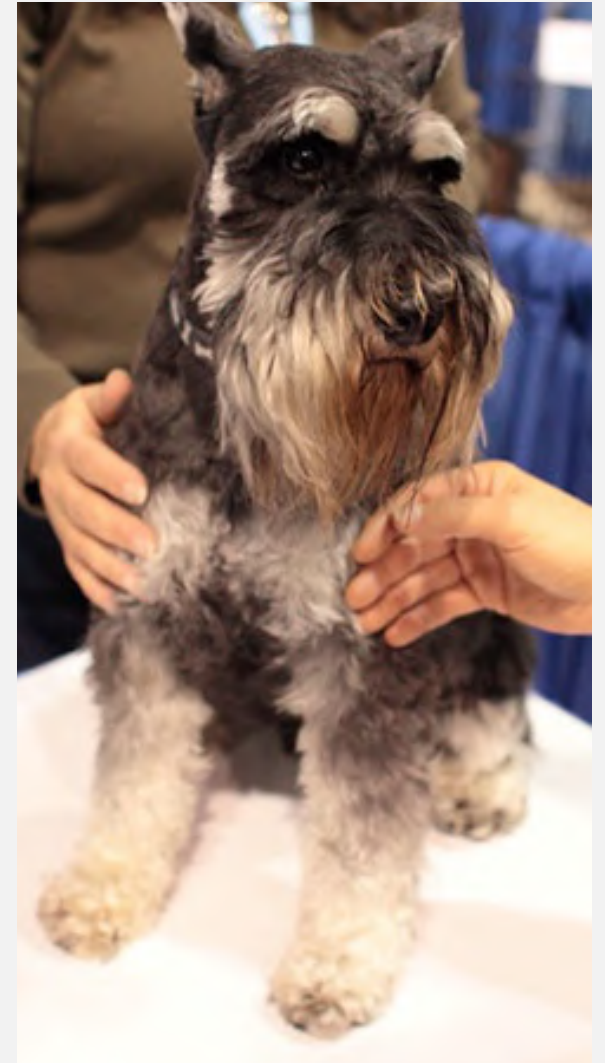
- Infectious
 - Parasitism, Fungal diseases
- Inflammatory
 - IBD/lymphangiectasia
 - Hypersensitivity (i.e. food allergies)
- Obstructive
 - Neoplastic disease
 - Hypertrophic disease
- Drugs

NON-GI ORIGIN

- CKD
- Hepatic disease
- Pancreatitis
- Addison's disease
- CNS disease
- Drugs
- DKA

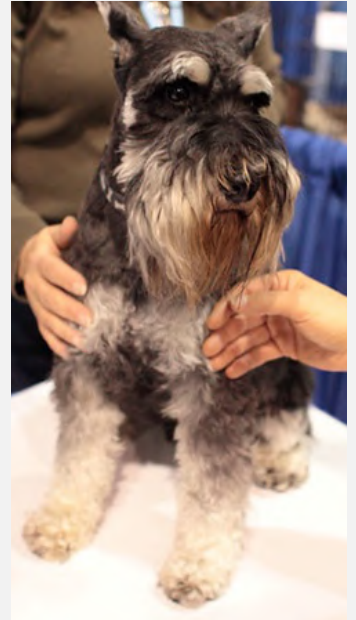
DIESEL

- 8-year-old MN Miniature Schnauzer
 - Chronic vomiting (9 month duration)
- Originally seen 6 months prior
 - Owners did not want to pursue biopsies at that time
 - AUS noted mild GI thickening
 - Presumptively diagnosed with IBD
 - Treated with prednisone
 - Initially responded, however the vomiting returned over time
- Treated with Cerenia
 - Initially controlled the vomiting, but now is not helping
 - Owners currently only given 1x per week for some reason....



DIESEL

- Yesterday he vomited
 - Some blood
 - Didn't finish breakfast, which is very unlike him
- Physical Exam
 - TPR = normal
 - Really nothing else remarkable outside of some dental tartar/halitosis
 - Abdominal palpation soft and non painful
 - Rectal exam unremarkable



DIESEL

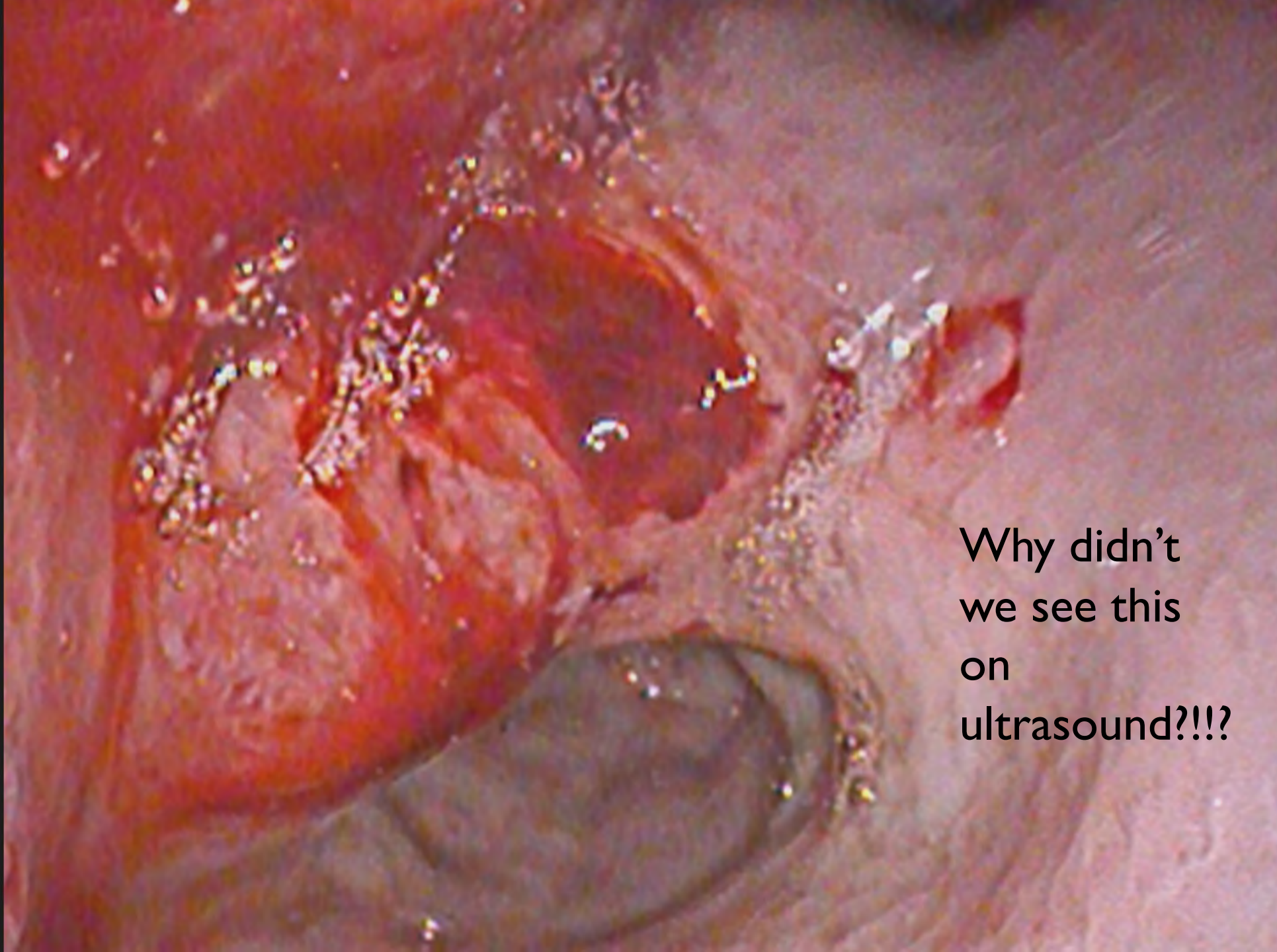
- Recommended lab work
 - CBC
 - Biochemistry
 - UA (or USG)
- Recommended endoscopy
 - See what is going on
 - Collect biopsies

TEST	RESULT	REFERENCE VALUE	
RBC	7.56	5.65 - 8.87 x10 ¹² /L	
Hematocrit	0.492	0.373 - 0.617 L/L	
Hemoglobin	167	131 - 205 g/L	
MCV	65.1	61.6 - 73.5 fL	
MCH	22.1	21.2 - 25.9 pg	
MCHC	339	320 - 379 g/L	
RDW	20.1	13.6 - 21.7 %	
% Reticulocyte	0.2	%	
Reticulocyte	17.4	10 - 110 K/μL	
WBC	7.44	5.05 - 16.76 x10 ⁹ /L	
% Neutrophil	76.1	%	
% Lymphocyte	8.3	%	
% Monocyte	6.6	%	
% Eosinophil	8.3	%	
% Basophil	0.7	%	
Neutrophil	5.66	2.95 - 11.64 x10 ⁹ /L	
Lymphocyte	0.62	1.05 - 5.10 x10⁹/L	L
Monocyte	0.49	0.16 - 1.12 x10 ⁹ /L	
Eosinophil	0.62	0.06 - 1.23 x10 ⁹ /L	
Basophil	0.05	0.00 - 0.10 x10 ⁹ /L	
Platelet	380	148 - 484 x10 ⁹ /L	
PDW	12.8	9.1 - 19.4 fL	
MPV	10.0	8.7 - 13.2 fL	
Plateletcrit	0.38	0.14 - 0.46 %	

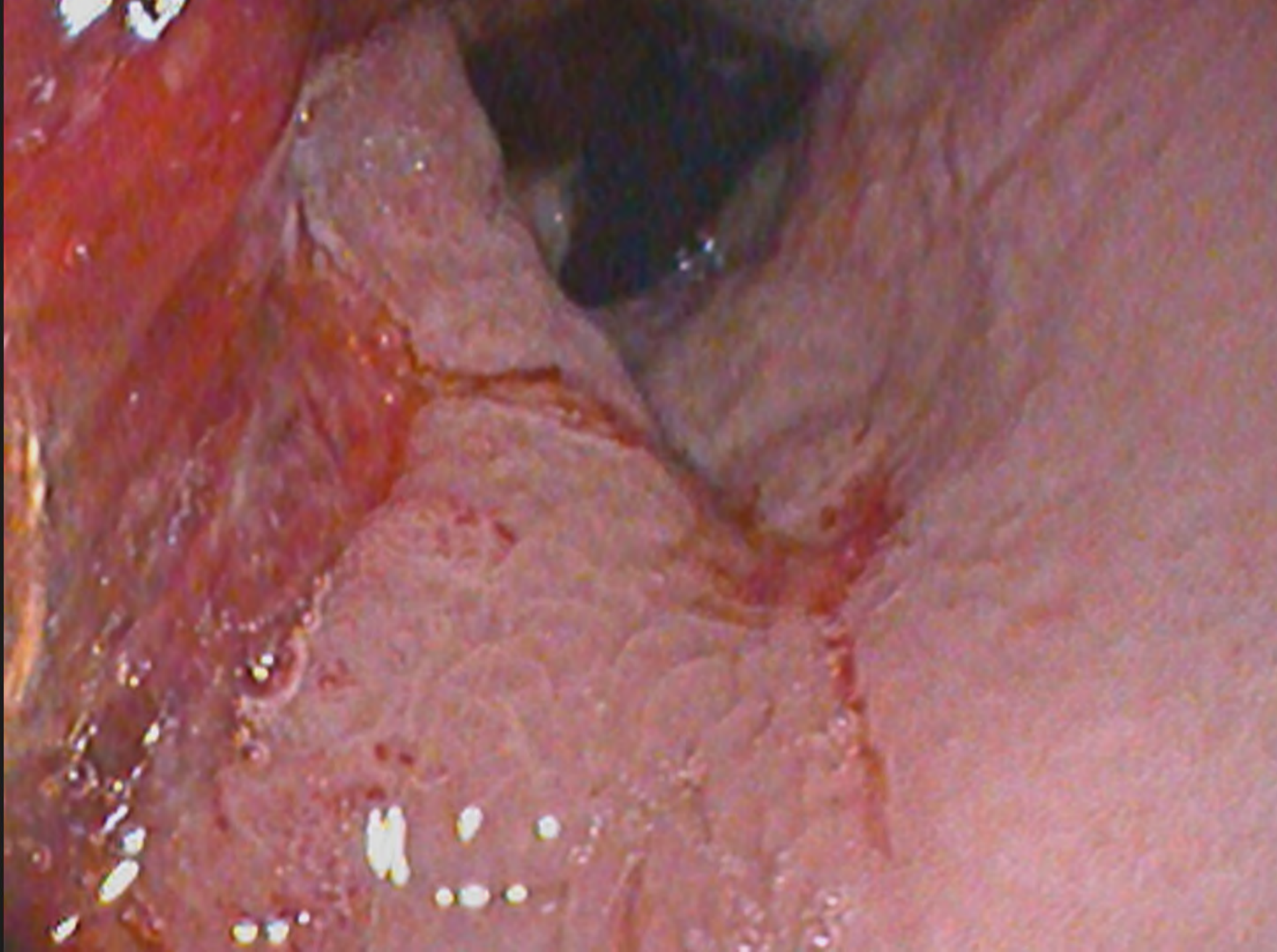
DIESEL

- Chemistry Panel
- Really boring!
 - Proteins normal
 - Cholesterol normal
 - Calcium normal
 - No renal or hepatic changes

TEST	RESULT	REFERENCE VALUE	
Glucose	5.70	4.11 - 7.95 mmol/L	
Creatinine	112	44 - 159 µmol/L	
Urea (BUN)	5.1	2.5 - 9.6 mmol/L	
BUN: Creatinine Ratio	11		
Phosphorus	1.12	0.81 - 2.20 mmol/L	
Calcium	2.54	1.98 - 3.00 mmol/L	
Sodium	149	144 - 160 mmol/L	
Potassium	4.6	3.5 - 5.8 mmol/L	
Na: K Ratio	32		
Chloride	114	109 - 122 mmol/L	
Total Protein	67	52 - 82 g/L	
Albumin	31	23 - 40 g/L	
Globulin	36	25 - 45 g/L	
Albumin: Globulin Ratio	0.9		
ALT	22	10 - 125 U/L	
ALP	34	23 - 212 U/L	
GGT	0	0 - 11 U/L	
Bilirubin - Total	<2	0 - 15 µmol/L	
Cholesterol	5.12	2.84 - 8.26 mmol/L	
Osmolality	296	mmol/kg	



Why didn't
we see this
on
ultrasound???



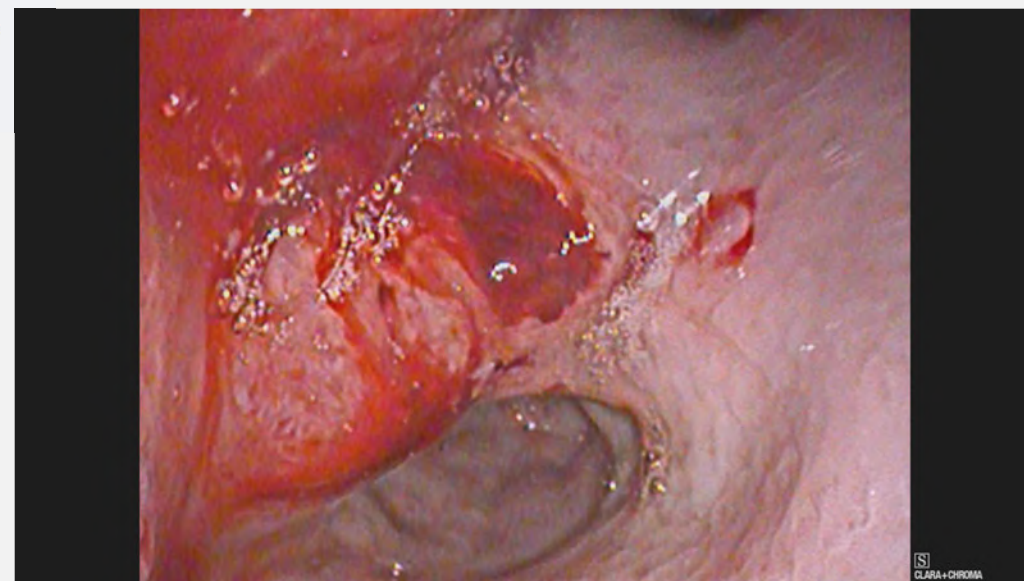
Slide C, gastric wall mass, 5 pieces. The specimen consists of gastric mucosa. In one piece of tissue there is a dense infiltrate of inflammatory cells consisting primarily of neutrophils with aggregates of erythrocytes and fibrin. In 2 pieces of tissue glands are irregularly separated by mildly to moderately edematous supporting lamina propria. There are small infiltrates of small lymphocytes and plasma cells. In 2 pieces of tissue normal glandular architecture has been disrupted by a neoplastic infiltrate. The neoplastic cells are similar in appearance to the neoplastic tissue seen on slide A.

MICROSCOPIC INTERPRETATION:

Stomach: Moderate multifocal lymphocytic, plasmacytic gastritis with edema and lymphoid hyperplasia

Gastric wall mass: Gastric carcinoma

Small intestine: Slight to moderate plasmacytic, lymphocytic enteritis





Perioperative complications and outcome after surgery for treatment of gastric carcinoma in dogs: A Veterinary Society of Surgical Oncology retrospective study of 40 cases (2004–2018)

Using Cox proportional hazards regression analysis

Results: Surgical treatment included partial gastrectomy (28 dogs), Billroth I (9 dogs), subtotal gastrectomy (2 dogs), and submucosal resection (1 dog). Major postoperative complications occurred in 8 of 40 dogs, including septic peritonitis secondary to dehiscence in 4 dogs. The median progression free interval was 54 days, and the median survival time (MST) was 178 days (range, 1–1902). According to multivariable analysis results, experiencing an intraoperative complication was associated with an increased risk of death (hazard ratio [HR] 3.5, 95% CI 1.1–9.8, $P = .005$), and administration of adjuvant chemotherapy correlated with an improved survival (HR 0.4, 95% CI 0.2–0.9, $P = .03$).

Conclusion: In this population of dogs, MST exceeded historically reported data, major postoperative complication rates were comparable to established literature, and administration of adjuvant chemotherapy was associated with improved survival.

20% had major post op complications

Those that got “chemo” tended to survive longer
No single protocol and cases were highly variable

Comparison of body condition score and other minimally invasive biomarkers between dogs with gastric carcinoma and dogs with chronic gastritis

Concentrations were compared among the 3 groups.

RESULTS

Dogs with gastric carcinoma were significantly older and had a significantly lower BCS, lower serum folate concentration, and greater serum C-reactive protein (CRP) concentration, compared with dogs with chronic gastritis and control dogs.

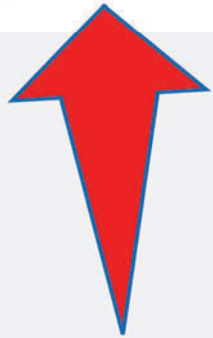
CONCLUSIONS AND CLINICAL RELEVANCE

Results suggested that age > 8 years, BCS < 4, serum CRP concentration > 25 mg/L, and an abnormally low serum folate concentration might be useful noninvasive biomarkers for identification of dogs with gastric carcinoma. For underweight older dogs with signs of upper gastrointestinal tract disease and high serum CRP and low serum folate concentrations, gastric biopsy specimens should be obtained and evaluated so that a prompt definitive diagnosis can be made and appropriate treatment initiated. (*J Am Vet Med Assoc* 2019;254:226–235)

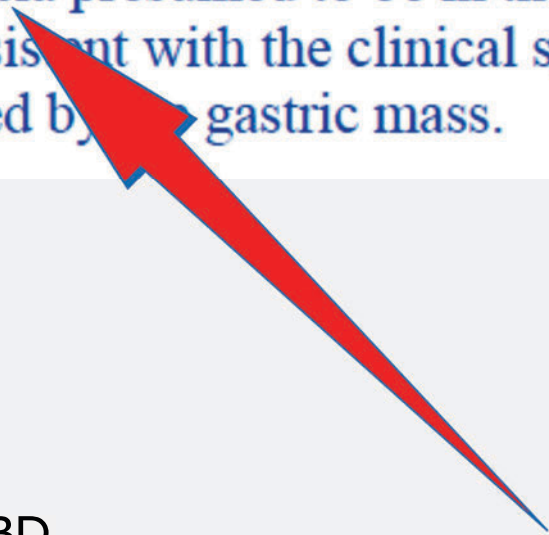
These dogs tend to be older, in thinner BCS and have higher C Reactive Protein than IBD patients

WHY DO WE TAKE SO MANY BIOPSIES?

The gastric wall mass is consistent with a neoplasm arising from mucosal glands. There is a focal aggregate of inflammatory cells suggesting ulceration. Nonneoplastic areas of the stomach are variably inflamed with regions of edema. Hyperplasia presumed to be in the area of the pylorus is also present. The cellular infiltrate in the small intestine is consistent with the clinical syndrome of inflammatory bowel disease, but may also be secondary to irritation caused by the gastric mass.



There is some evidence of IBD,
but it is secondary to the mass!



Hyperplasia of the pyloric
antrum can also contribute
to vomiting

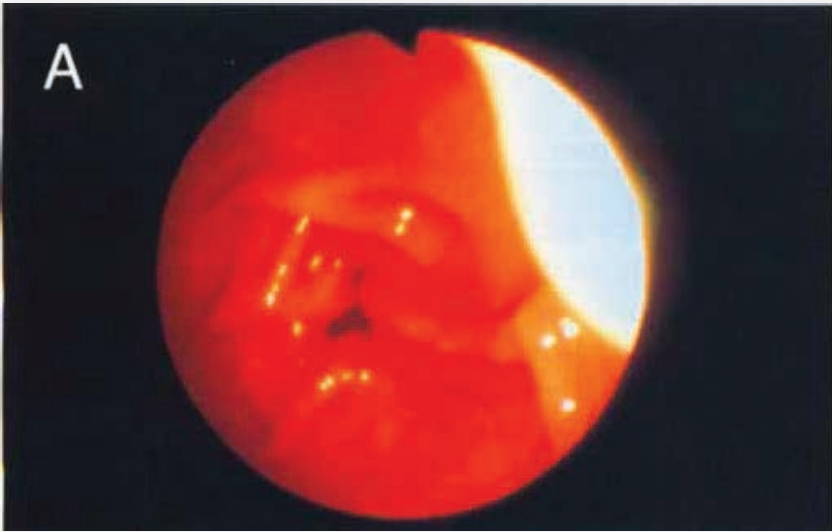
PYLORIC HYPERTROPHY

- Chronic hyperplastic pyloric gastropathy occurs most commonly in middle-aged small breed dogs
 - Think little poodles...
- Clinical signs:
 - Vomiting, weight loss
- Diagnosis
 - Used to be with barium radiographs and abdominal exploratory for full thickness biopsies
- Endoscopy
 - Can make a visual diagnosis and biopsy mucosa to rule out neoplastic disease

Endoscopic Diagnosis of Chronic Hypertrophic Pyloric Gastropathy in Dogs

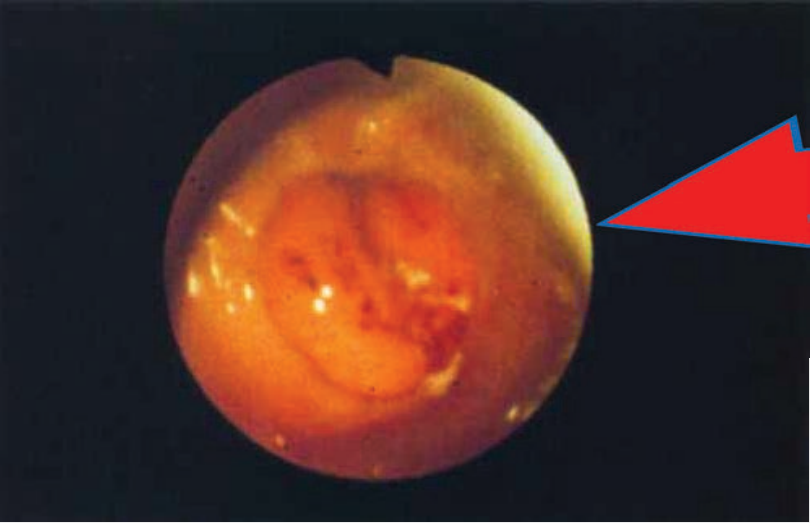
Michael S. Leib, DVM, MS, Geoffrey K. Saunders, DVM,
Martha L. Moon, DVM, MS, Mary Ann Mann, DVM,
Robert A. Martin, DVM, Michael E. Matz, DVM,
Beverlee Nix, DVM, Mark M. Smith, VMD, and Don R. Waldron, DVM

The endoscopic appearance of chronic hypertrophic pyloric gastropathy (CHPG) in five dogs is described. Several patterns of enlarged mucosal folds that surrounded and obstructed the pyloric canal were observed. Initially, endoscopically obtained biopsy samples of mucosa were judged to be histologically normal. Diagnosis of CHPG was confirmed and relief of pyloric obstruction accomplished at exploratory laparotomy (in four dogs). Retrospective evaluation of pyloric tissue samples, obtained during endoscopy, identified subtle histological characteristics of CHPG. Gastric and duodenal neoplasia or antral polyps can mimic the endoscopic appearance of CHPG but can be differentiated based on their endoscopic and histological appearance. These cases show that endoscopic examination is a valuable procedure for the diagnosis of CHPG in dogs that chronically vomit. (Journal of Veterinary Internal Medicine 1993; 7:335-341. Copyright © 1993 by the American College of Veterinary Internal Medicine.)



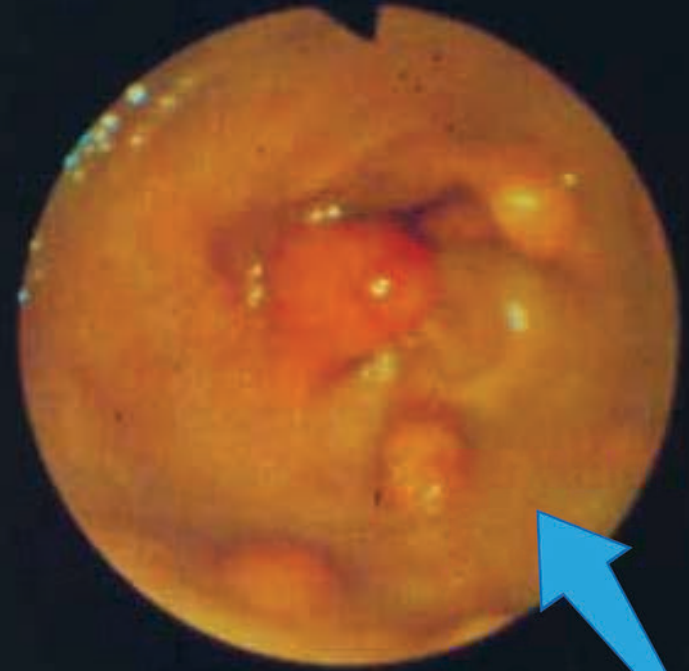
Normal pylorus – A = closed, B = open

Dogs with pyloric hypertrophy





Duodenal lymphoma can cause protrusion of the pylorus in the stomach and mimic hypertrophy



Gastric polyps



Multiple masses in the antrum:
Brush cytology = mast cell tumour

DUKE

- 3 year old MN Bloodhound
- Waxing and waning “swallowing” issues
 - exaggerated swallowing, extends his neck
- Sometimes decreased appetite, sometimes lethargic
 - Owner says he is better on a home cooked diet with a lot of broth
- Chronic soft cough
- Previously Meds: meloxicam and prednisone (separately)
 - No improvement with either
- Physical Exam - TPR normal, 48kg

DUKE - DIAGNOSTICS

- CBC – Completely normal
- Superchem – Completely normal
- UA – unremarkable, USG 1.020
- Cortisol – 134 (slightly elevated)
- Abdominal Ultrasound – essentially normal
- SNAP 4Dx – negative x4
- Thoracic radiographs – mild to moderate amount of gas in the esophagus

Patient Info:

Name: Duke
Chart No: 20000814
Owner: Mulligan-Smith
Doctor: Dr. Casey Gaunt

Species: Canine
Breed: Bloodhound
Age: 3Y
Sex: CM

Hospital:

Guardian Veterinary Centre
 5620-99TH ST NW
 EDMONTON, AB T6E 1V2
Antech ID: 600225

Lab:

ANTECH Diagnostics Canada
 Clinical Skills Bldg, Rm 141,
 Calgary, Alberta T3R 1J3
Reported: 02/25/19 11:37
Received: 02/25/19

Accession No.	Doctor	Owner	Pet Name						
CYAA04135055	Dr. Casey Gaunt	Mulligan-Smith Megan	Duke	Test	Results	Adult Reference Range	L	Normal	H
Superchem									
Total Protein	62	50-74 g/L							
Albumin	38	27-44 g/L							
Globulin	24	16-36 g/L							
Albumin/Globulin Ratio	1.6	0.8-2.0 Ratio							
AST (SGOT)	32	15-66 U/L							
ALT (SGPT)	60	12-118 U/L							
Alkaline Phosphatase	29	5-131 U/L							
GGTP	1	1-12 U/L							
Bilirubin, Total	2.3	0.0-5.1 umol/L							
BUN	9.3	2.1-11.1 mmol/L							
Creatinine	106	44-141 umol/L							
Bun/Creatinine Ratio	88	Ratio							
Phosphorus	1.24	0.81-1.94 mmol/L							
Glucose	5.7	3.9-7.7 mmol/L							
Calcium	2.63	2.23-2.85 mmol/L							
Magnesium	0.8	0.7-1.3 mmol/L							
Sodium	150	139-154 mmol/L							
Potassium	4.1	3.6-5.5 mmol/L							
Sodium/Potassium Ratio	37	27-38 Ratio							
Chloride	114	102-120 mmol/L							
Cholesterol	5.09	2.38-10.0 mmol/L							
Triglycerides	0.36	0.33-3.32 mmol/L							
Amylase	619	290-1125 U/L							
PrecisionPSL	25	24-140 U/L							
Pancreatitis is unlikely, but a normal PrecisionPSL result does not completely exclude pancreatitis as a cause for gastrointestinal signs.									
CPK	91	59-895 U/L							
Comment(s) Hemolysis 2+ No significant interference.									

Test	Results	Adult Reference Range	L	Normal	H	Urinalysis	
Complete Blood Count						Collection Method	
WBC	7.5	4.0-15.5 10 ⁹ /L				Natural Voiding	
RBC	7.1	4.8-9.3 10 ¹² /L				Color	Yellow
Hemoglobin	173.0	121-203 g/L				Appearance	Cloudy *Clear
Hematocrit	50	36-60 %				Specific Gravity	1.020 1.015-1.050
MCV	71	58-79 fL				pH	6.0 5.5-7.0
MCH	24.5	19-28 pg				Protein	Negative Neg
MCHC	346	300-380 g/L				Glucose	Negative Neg
Platelet Count	252	170-400 10 ⁹ /L				Ketone	Negative Neg
Platelet Estimate	Adequate	Adequate				Bilirubin	Negative Neg To 1+
Differential						Blood	Negative Neg
	Absolute	%				WBC	0-1 0-3 HPF
Neutrophils	5.93	79 2.06-10.60 10 ⁹ /L				RBC	None 0-3 HPF
Lymphs	1.20	16 0.69-4.50 10 ⁹ /L				Casts	None Seen LPF
Monocytes	0.38	5 0-0.84 10 ⁹ /L				Struvite Crystals	0-1 HPF
Eosinophils	0.00	0 0-1.20 10 ⁹ /L				Bacteria	None Seen None HPF
Basophils	0.00	0 0-0.15 10 ⁹ /L				Transitional Epithelia	0-1 None-Rare HPF
Blood Parasites	None Seen					Fat Droplets	0-1 None HPF
RBC Comment	Normal						

Cortisol

Tube Labeled

Resting

Cortisol Sample 1 ACTH 134

28-124 nmol/L

HIGH

DUKE ENDOSCOPY

- Oropharynx and Larynx– normal
- Esophagus – Normal appearance, no esophagitis or ulceration
- LES – wide open, with rugal folds visible protruding into the esophagus
- Stomach – Antral region with erythema and yellow discoloration
- Duodenum – Moderate amount of fluid present and limited peristalsis noted during exam
- Biopsies collected from stomach and duodenum



WHAT WE DID NOT SEE

- Gastric Ulcer
- Secondary to meloxicam
 - Dog got an accidental double dose
- I frequently blame NSAIDs got GI ulceration and bleeding in dogs
- Remember these are only for HEALTHY animals!



DUKE - INITIAL THERAPY

- Metoclopramide
 - 10mg PO TID
 - Goal is to increase lower esophageal sphincter tone and improve gastric/proximal SI motility
- Omeprazole
 - 40mg PO BID
 - Goal is to increase the gastric pH to decrease esophageal irritation secondary to reflux through the open LES

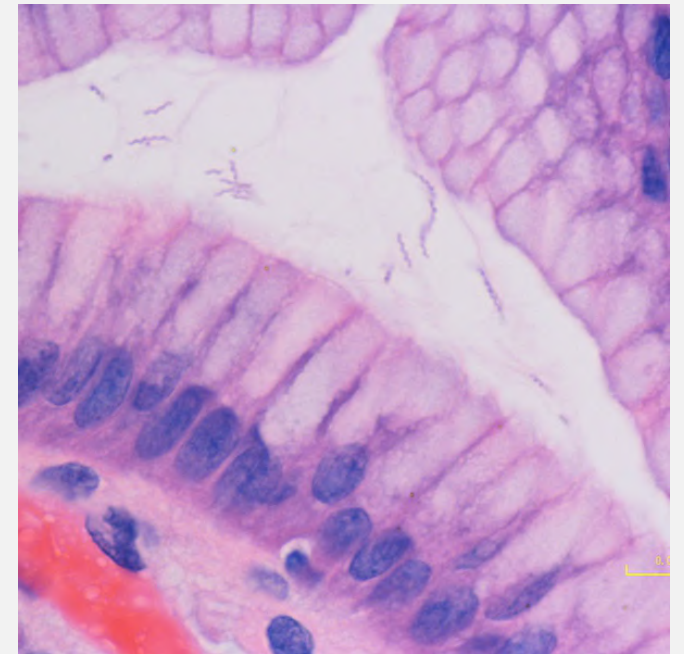
HISTOPATHOLOGY

MICROSCOPIC FINDINGS:

- Stomach: Gastritis, lymphoplasmacytic, mild to moderate, chronic, with mild congestion, edema, scant to mild superficial hemorrhage; spiral bacilli consistent with *Helicobacter* sp.
- Moderate to large numbers of spiral bacilli consistent with *Helicobacter* sp. are noted.
 - Found within the crypts
 - Sometimes associated with chronic gastroenteritis
 - Also been found in dogs and cats without clinical disease.
- Duodenum: Enteritis, lymphoplasmacytic, mild to moderate, chronic, with mild segmental erosion, congestion, and edema

HELICOBACTER SPP

- Gram negative curved to spiral bacteria
 - Contain lots of urease (helps them alter the gastric pH so they can live)
 - MANY different species...
- Diagnosed on histo or cytology (gastric brushing)
- Much debate as to whether this is a primary cause of disease
 - Contributing factor?
 - Result of other underlying disease?
 - Different than disease in people



HELICOBACTER: TREAT OR NOT?

- I do think this is clinically relevant in *some* of our patients
- When do I treat?
 - If identified in large amounts on my biopsy samples
 - If clinical signs are predominately vomiting
 - If large amount of "bile staining" noted during endoscopy
 - If clients can't afford endoscopy and other practical causes of vomiting ruled out
 - Proper deworming
 - Diet trial
 - No systemic disease

HELICOBACTER: HOW TO TREAT

- Several different protocols available (CVT 15 a good resource)
- My preferred concoction:
 - Amoxicillin 15-20mg/kg PO BID x 14 days
 - Metronidazole 10mg/kg PO BID x 14 days
 - Bismuth subsalicylate (all PO BID x 14 days):
 - <5kg = 65.5mg
 - 5-10kg = 131mg
 - 10-25kg = 262mg
 - >25 kg = 525mg

DUKE: TREATMENT

The biopsy results from his stomach and small intestine noted mild inflammation, but a moderate to large amount of helicobacter. Now I do not typically treat small amounts of helicobacter that we see, however, given Duke's nebulous clinical signs and unimpressive gastric inflammation, I feel like it would be reasonable to treat him for 2 weeks with the following combination:

- 1) Amoxicillin 1000mg PO BID for 14 days
- 2) Metronidazole 500mg PO BID for 14 days
- 3) Pepto Bismol Maximum Strength 1mL PO BID for 14 days

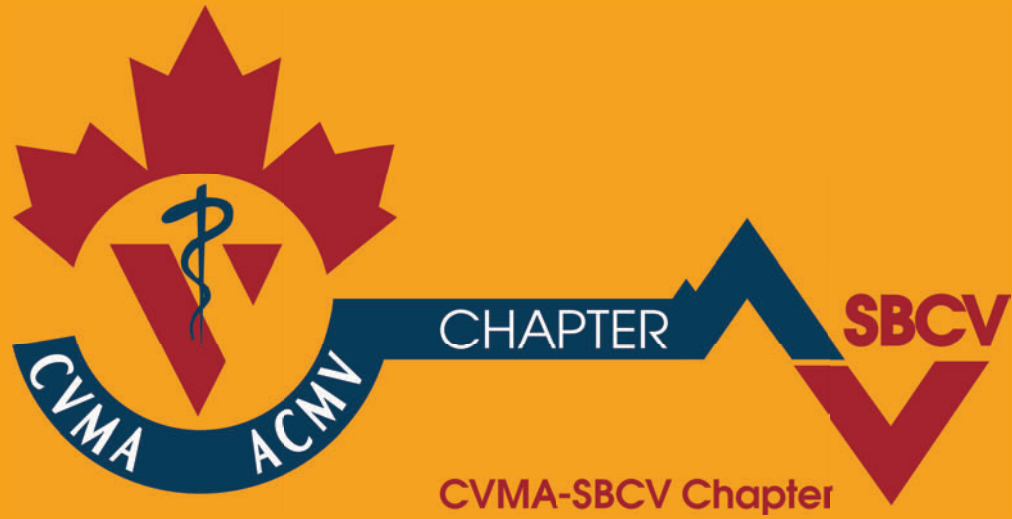
I have instructed Duke's owner to purchase the Pepto on her own. As we discussed on the phone, it would be great if you could get together the amoxicillin and metronidazole for her and have someone from your clinic call her when it is ready.

These medications should be in addition to the metoclopramide and omeprazole that Duke was originally discharged with. The metoclopramide was intended to help with the perception of decreased GI motility, which may be playing a role in the mild gastroesophageal intussusception that was noted during endoscopy. That can continue indefinitely if Duke's owner feels that has helped his clinical signs.

If Duke's clinical signs have improved after treatment of the helicobacter, then perhaps we do not need to do anything further. If his signs do not resolve, then we may need to consider revisiting the gastroesophageal intussusception that I saw during the scoping.

DUKE: OUTCOME

- Owner reported fewer “swallowing” episodes after starting the metoclopramide and omeprazole
- After the 2 week treatment for helicobacter, owner reported significant improvement:
 - Increased activity level
 - Strong appetite
 - No swallowing episodes
- Long term recommendation:
 - Remain on metoclopramide and omeprazole
 - Nutrition consult for a hypoallergenic diet



QUESTIONS?

Thank you all for listening and to the SBVC for inviting me to speak

DIARRRHEA



Fecal Scoring Chart

SCORE	SPECIMEN EXAMPLE	CHARACTERISTICS
1		<ul style="list-style-type: none"> • Very hard and dry • Often expelled as individual pellets • Requires much effort to expel from body • Leaves no residue on ground when picked up
2		<ul style="list-style-type: none"> • Firm, but not hard, pliable • Segmented in appearance • Little or no residue on ground when picked up
3		<ul style="list-style-type: none"> • Log shaped, moist surface • Little or no segmentation • Leaves residue on ground, but holds form when picked up
4		<ul style="list-style-type: none"> • Very moist and soggy • Log shaped • Leaves residue on ground and loses form when picked up
5		<ul style="list-style-type: none"> • Very moist, but has a distinct shape • Present in piles rather than logs • Leaves residue on ground and loses form when picked up
6		<ul style="list-style-type: none"> • Has texture, but no defined shape • Present as piles or spots • Leaves residue on ground when picked up
7		<ul style="list-style-type: none"> • Watery • No texture • Present in flat puddles

FIGURE. Fecal scoring chart. Reprinted with permission from Purina (purina.com)

ALL DIARRHEA IS NOT EQUAL...

ACUTE DIARRHEA

- Self-limiting vs. Life Threatening
 - Life threatening gets you to the ER!
- Empirical therapy appropriate
 - Easily digestible/bland diet
 - Empirical deworming
 - Empirical treatment
 - Metronidazole...

CHRONIC DIARRHEA

- This is where IM specialists can help
- Means its time to start running tests!
 - Usually after routine empiric measures have failed
 - Means patients ready for the next line of diagnostics
- Clients are usually more motivated to find an answer
- Makes risks of testing more reasonable

SMALL BOWEL VS LARGE BOWEL

Clinical Sign	Small Bowel	Large Bowel
Weight Loss	Yes	No
Frequency	Normal to slight increase	Marked Increase
Volume	Normal to increased	Small
Tenesmus	No	Yes
Mucous	No	Yes
Blood	None or Melena	Hematochezia (frank blood)
Vomiting	+/-	+/-

WHY DO WE LOCALIZE?

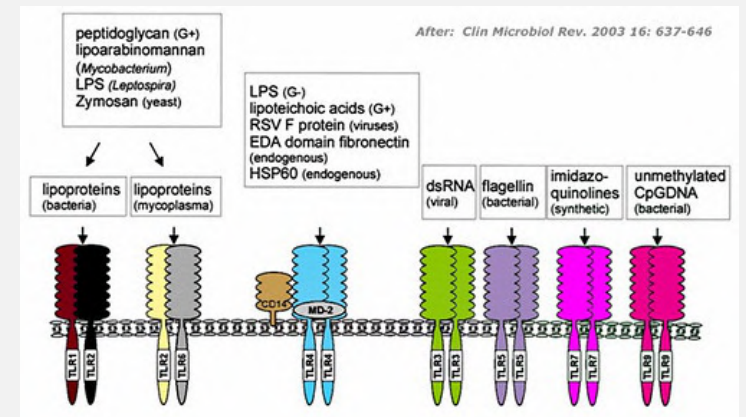
- Differentials
 - Some diseases more specific to small vs large
 - Parasitism, neoplastic disease (i.e. polyps), digestion/absorption issues (i.e. EPI)
- Diagnostics
 - Options for collecting samples
 - Endoscopy vs. surgery
- Treatments
 - Which drugs go to what areas?
 - Diets – allergies vs digestibility

INFLAMMATORY BOWEL DISEASE

- Not a single disease – this is a group of disorders
 - Histologic evidence of inflammation in the lamina propria of the SI, LI or both
- Chronic, persistent or recurrent GI signs
- A diagnosis of exclusion – immune-mediated gastroenteritis
 - We systematically eliminate the causes of GI inflammation
- There is rarely a single cause:
 - Host genetics
 - Environment
 - Intestinal mucosal immune system
 - Patient microbiota

IBD GENETICS

- There is not a single mode of inheritance that has been found responsible
 - Mutations in Toll-like and NOD-like receptors
 - Pattern recognition receptors of innate immunity
 - TLR4 and TLR5 polymorphisms in GSDs
 - TLR5 in a heterogenous population of dogs...
 - Mutations in autophagy proteins
- Mutated receptor leads to perception of commensal bacteria being recognized as a pathogen



INTESTINAL MUCOSAL IMMUNE SYSTEM

- Increased numbers of CD4+ and Ig producing plasma cells and T cell subsets support the idea that impaired immunoregulation is a factor in IBD
- These cells may also produce inappropriate cytokines
- May skew the immune response to a proinflammatory state
- Good evidence in humans
- Some evidence in dogs and cats as well

INTESTINAL MICROBIOTA

- A HUGE area of investigation in both human and animal GI disease
- Finding out what “normal” is can be daunting
 - Need this to compare to sick or “abnormal” patients
- Dysbiosis allowing “overgrowth” of some organisms
 - I.e. Enterobacteriaceae and *clostridium spp.*
 - May be different in different breeds (i.e. GSDs)
- Will likely be a rapidly changing area for us in the future

CLASSIFICATIONS OF IBD

- Food responsive enteropathy
- Antibiotic responsive enteropathy
- Immunosuppressive responsive enteropathy
 - True inflammatory disease based on histopath:
 - Lymphoplasmacytic
 - Eosinophilic
 - Granulomatous
- Breed specific disorders



Enteropathy:

- We use this term because it is more inclusive than just saying “diarrhea” or vomiting”
- Helps to explain the diffuse and often changing nature of the clinical signs

FOOD RESPONSIVE ENTEROPATHY



The most common cause of diarrhea!!!



Allergies vs intolerance



What does a proper diet trial look like?

Contents
Duration
Response



Novels proteins vs hydrolyzed proteins



Homemade diets

Use a nutritionist!!!



DIETARY MANAGEMENT OF IBD



- Allergies vs. Intolerances
 - Allergies = an inflammatory response triggered by a component of the food
 - Typically associated with the protein component in Dogs/cats
 - Chicken and Beef frequently implicated, but not the only possibilities
 - Intolerance = inability to process and/or absorb a component of the food
 - I.e. gluten - occurs in some breeds (Soft-coated Wheaten)
 - Fat malabsorption - i.e. lymphangiectasia
 - Fibre restriction – in patients with excessive bloating/flatulence
 - Low vs medium vs high fermentability of fibres





DIETARY MANAGEMENT OF IBD



NOVEL PROTEIN SOURCE

- A protein source that the patient has not been exposed to before
- Can be difficult in some patients
- Theory:
 - Decreases antigenic stimulation of inflammatory response

HYDROLYZED PROTEIN SOURCE

- Smaller proteins that evade detection by the immune system to reduce inflammatory response
- Easy option
- Price concerns?
- Palatability concerns?



DIET TRIALS

- Who benefits?
 - Reasonable to try in all stable dogs and cats with chronic GI signs
 - One study suggested that younger animals are more likely to respond
 - But really can be any age/breed
- How long?
 - Should see at least some improvement within 1-2 weeks if they are going to respond
 - Continue for 10-12+ weeks to see full improvement
- Forever!?
 - Many dogs can be transitioned back to a “normal diet”, but I typically recommend to stay on it for life



TREATS



- Owners can't live without treats (pets do just fine!)
- Can buy hypoallergenic treats
- Can use other foods – non protein containing
 - Baby carrots, green beans
 - Apple slices, banana slices
 - Ice cubes
- Portion out part of the hypoallergenic diet that they select



HOMEMADE DIETS

- These can be incredibly helpful!
 - Can account for multiple medical disorders at once
 - CKD + food allergies
 - Extreme fat restriction + CKD
- Involves owners in the process and gives them something to obsess over!
- **MAKE THIS EASY ON YOU!**
 - Use a veterinary nutrition service – there are many available, some for free!

NUTRITION SERVICE EXAMPLE

<https://www.vetmed.ucdavis.edu/hospital/small-animal/nutrition>

There are two portions to the consult request:

- 1) History for the owner to complete
- 2) Medical portion for the veterinarian to complete

It does cost money – which can encourage owners to actually adhere to the plan!

The following is the daily recipe for a therapeutic home-cooked diet for Dog Jones:

INGREDIENT (substitutions are not possible; for example, exact cut of meat and cooking method will be specified)	AMOUNT
- Specific protein source	xxx grams, cooked amount
- Specific carbohydrate source	xxx grams, cooked amount
- Specific fat source 1	xxx grams (xxx teaspoons)
- Specific fat source 2	xxx grams (xxx teaspoons)
Supplement (often up to 4-8 different products; exact brands must be used when specified)	
- Supplement product 1	xxx teaspoon
- Supplement product 1	xxx tablets
- Supplement product 1	xxx tablets

Nutrient Composition (on ME basis*):

xx% Protein, xx% Fat, xx% Carbohydrate. Total energy: xxx kcal per day.

Concentrations of selected relevant nutrients will be provided here.

**Please note that the percentage on a metabolizable energy (ME) basis is not equivalent to the percentage on an "as is" or "as fed" basis found on pet food labels. Comparing on a ME basis allows nutritionists to compare diets that may vary in fiber, ash, moisture, or caloric density more precisely.*

Cooking instructions

Details for preparing the diet will be in this section. Specific cooking and feeding instructions will be provided. Different foods have different nutritional profiles; the recipe and cooking instructions must be followed exactly. A kitchen scale and measuring spoons will be needed.

Storage instructions

Storage instructions will be provided in this section.

Supplements

Information regarding supplements will be provided in this section.

Treats

If other foods are part of the individual patient's nutritional management plan, we can provide a treat allowance that can accommodate snacks, the need to give medications, or to add variety to the daily meals. If possible, the treat allowance can be used to add different foods to each meal depending on availability, season, what the pet likes, and to provide variety to the diet. A list of appropriate foods will be provided.

Follow up and monitoring

Instructions for recheck veterinary examinations will be provided in this section. Monitoring body weight is an important aspect of this so that the correct amount of food is provided to meet the individual patient's needs.

Please see the FAQ for more detailed information about our services.

ANTIBIOTIC RESPONSIVE ENTEROPATHY

- What does this mean?
 - Acute or chronic diarrhea that responds when treated with antibiotics
 - But not just ANY antibiotic...
- Acute Infectious processes
 - *Campylobacter, salmonella, enteropathogenic e. coli*
- Dysbiosis/SIBO
- IBD
 - Tylosin-responsive diarrhea
 - Granulomatous colitis

WHEN DOES “ARE” HAPPEN?

- As a result of other underlying disease or treatment
 - IBD
 - Secondary to another infection
 - Treatment with antibiotics
 - Treatment with acid suppressing medications (H₂ blockers, PPIs)
- How do we diagnose it?
 - There is no test...
 - Perhaps the best is identifying neutrophilic inflammation on intestinal biopsy samples
 - Culture
 - Difficult to accurately collect and even more difficult to interpret
 - Molecular diagnostics are not widely available or easy to interpret

ARE: TREATMENT

- What drugs are we talking about?
 - Not random antibiotics!
 - Metronidazole
 - Long thought to have immunomodulatory properties
 - Excellent anaerobic spectrum
 - 10 mg/kg PO BID
 - Tylosin



WHAT IS TYLOSIN?

- Macrolide antimicrobial
 - Bacteriostatic
 - Activity against most gram-positive & gram-negative cocci, gram positive rods & *Mycoplasma*
 - *E. coli* and *Salmonella spp.* intrinsically resistant
 - Anti-inflammatory?
 - Different mechanism than glucocorticoids
- Veterinary only drug
 - Chickens and pigs
 - Powder form – often need to compound into capsules
 - Europe has a tablet

TYLOSIN RESPONSIVE DIARRRHEA

- Signalment:
 - Often young to middle age dogs
 - Tend toward medium to larger breeds
- Clinical Signs:
 - Often intermittent but progressively become more frequent
 - Watery and/or mucousy feces (so more mixed bowel in nature)
 - Increased borborygmus and flatulence
 - Occasionally vomiting during the episodes
- Diagnostic Testing:
 - Routine lab work unremarkable
 - Fecal testing negative
- Imaging
 - Often unremarkable
- Biopsies
 - Little to no inflammation on histo

**These are
NOT super
sick dogs!**

WHEN TO USE TYLOSIN?

- After we rule out systemic causes of disease
 - CBC, biochemistry, urinalysis
 - Possible TLI
 - Possible infectious disease testing based on patient history
- After a negative fecal and/or appropriate deworming
 - 50mg/kg fenbendazole PO SID x 3 days (repeated in 3 weeks and maybe 3 months)
- After diet a trial
- BEFORE Endoscopy???
 - I often offer this as something to try before moving onto invasive and expensive testing
 - Response to treatment may help us avoid endoscopy

HOW TO USE TYLOSIN

- Dosing:
 - 10-15mg/kg PO BID or 25mg/kg PO SID
- Duration of therapy:
 - Dogs usually respond within 3-5 days of starting therapy
 - I treat for 10-14 days and then stop
 - Often resolves the diarrhea, especially in combination with a diet change
- Retreat?
 - If the signs recur, as they sometimes do several weeks later, can restart tylosin
 - Can be used long term
 - I have treated some patients for years (including my own dog!)
 - Taper gradually to find the lost dose/frequency that will control signs

IS LONG TERM TYLOSIN BAD?

- In truth, we do not yet know
- Antimicrobial resistance?
 - Given that we don't use tylosin clinically for other diseases in small animals, we haven't encountered it as a clinical problem
- We know it does change the microbiome:

to when they had diarrhoea following discontinuation of tylosin. In conclusion, cessation of diarrhoea in TRD dogs with tylosin treatment could be mediated by selection of a specific lactic acid population, the *Enterococcus* spp., due to their potential probiotic properties.



Oral tylosin administration is associated with an increase of faecal enterococci and lactic acid bacteria in dogs with tylosin-responsive diarrhoea



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BREED SPECIFIC DISORDERS

- German Shepherd Dogs
 - Multiple immune defects
- Primary idiopathic disease:
 - Norwegian Lundehunds, Maltese, Shar-peis, Yorkshire terriers
 - Severe changes in lymphatic vessels with development of lymphogranulomas around lymphatic vessels
- Soft Coated Wheaten Terriers
 - PLE, gluten intolerance
- Basenji's
 - Rare immunoproliferative enteropathy



BURTON

- 8 year old MN Cockapoo
- 6 week history of diarrhea
 - No blood, melena, mucous or straining
 - No weight loss
 - Larger volumes more frequently
 - Last few days has been *constant*
- Soft nonproductive cough for 4 weeks
- Always had a “sensitive” stomach
- Vaccines “UTD”, no travel, other dog in house is healthy, unknown deworming history



BURTON

- Saw 1 vet 1 week after the diarrhea began
 - Treated with doxycycline, metronidazole, metacam
 - No change to diarrhea
- Saw 2nd vet after the antibiotics were done:
 - Blood work
 - Marked panhypoproteinemia (Alb – 12, Glob – 13, TP – 25)
 - Thoracic radiographs
 - Marked pleural effusion
 - Started treatment with 10mg prednisone
 - Referred for further work up



INITIAL BLOOD WORK

- CBC – totally normal
- Urine – 1.025 USG
 - Quiet sediment
- Biochemistry
 - Panhypoproteinemia
 - Alb – 12
 - Glob 13
 - Hypocalcemia
 - Hyponatremia
 - Hypokalemia

HEMATOLOGY

TEST	RESULT	REF. RANGE/UNITS
RBC	6.5	5.0 - 12.0 x10 ¹² /L
Hematocrit	0.46	0.38 - 0.57 L/L
Hemoglobin	159	134 - 207 g/L
MCV	70.8	59.0 - 76.0 fL
MCH	24.5	21.9 - 26.1 pg
MCHC	345.7	326.0 - 392.0 g/L
RDW	14.5	10.0 - 19.0
% Reticulocyte	1.5	%
Reticulocytes	97.5	10.0 - 110.0 x10 ³ /uL
Reticulocyte Hemoglobin	29.0	22.3 - 29.6
WBC	13.1	4.9 - 17.6 x10 ⁹ /L
% Neutrophils	82.0	%
% Lymphocytes	12.6	%
% Monocytes	4.5	%
% Eosinophils	0.9	%
% Basophils	0.0	%
Neutrophils	10.7	2.9 - 12.7 x10 ⁹ /L
Lymphocytes	1.7	1.1 - 5.0 x10 ⁹ /L
Monocytes	0.6	0.0 - 1.2 x10 ⁹ /L
Eosinophils	0.1	0.0 - 1.5 x10 ⁹ /L
Basophils	0.0	0.0 - 0.1 x10 ⁹ /L
Platelets	257	143 - 448 x10 ⁹ /L

Platelet Comments Platelet assessment Adequate
No clumped platelets noted.

CBC Comment RBC, WBC, and platelet morphology normal

CHEMISTRY

TEST	RESULT	REF. RANGE/UNITS
Glucose	4.8	3.5 - 6.3 mmol/L
IDEXX SDMA ^a	10	0 - 14 ug/dL
L Creatinine	39	44 - 133 umol/L
Urea (BUN)	3.2	3.2 - 11.0 mmol/L

Phosphorus	1.0	0.8 - 2.0 mmol/L
L Calcium	1.6	2.2 - 2.8 mmol/L
L Sodium	141	142 - 152 mmol/L
L Potassium	3.7	4.0 - 5.4 mmol/L
H Na: K Ratio	38	28 - 37
Chloride	113	108 - 119 mmol/L
TCO2 (Bicarbonate)	23	13 - 27 mmol/L
L Anion Gap	9	11 - 26
Total Cations	145	mmol/L
Total Anions	136	mmol/L
L Total Protein ^b	25	55 - 75 g/L
L Albumin ^c	12	27 - 39 g/L
L Globulin	13	24 - 40 g/L
Albumin: Globulin Ratio	0.9	0.7 - 1.5
L ALT	6	18 - 121 IU/L
AST	40	16 - 55 IU/L
ALP	20	5 - 160 IU/L
Bilirubin - Total	0.7	0.0 - 5.2 umol/L
Bilirubin - Conjugated	0.1	0.0 - 3.4 umol/L
L Cholesterol	1.8	3.4 - 8.9 mmol/L
Amylase	1246	337 - 1469 IU/L
Lipase	182	138 - 755 IU/L
Creatine Kinase	144	10 - 200 IU/L
Osmolality	277	250 - 310 mmol/kg
Hemolysis Index	Normal	
Icterus Index	Normal	
Lipemia Index	Normal	
Spec cPL	54	0 - 200 ug/L

STABILIZED THROUGH ER SERVICE

- Thoracocentesis
 - Recovered a pure transudate, fits with the low albumin
- Blood Gas
- Abdominal Ultrasound:
 - **Intestines:** Colon 0.19 cm. Small Intestines 0.36 to 0.42 cm. The small intestinal mucosa is markedly hyperechoic with mucosal striae.
 - Pancreas: Right limb seen, normal size, shape and echogenicity
 - **Mesenteric Lymph nodes:** Mildly enlarged and hypoechoic jejunal lymph nodes.
 - **Other:** There is a small amount of free abdominal fluid. There is trace pleural effusion, and the tip of the right middle lung lobe is consolidated.

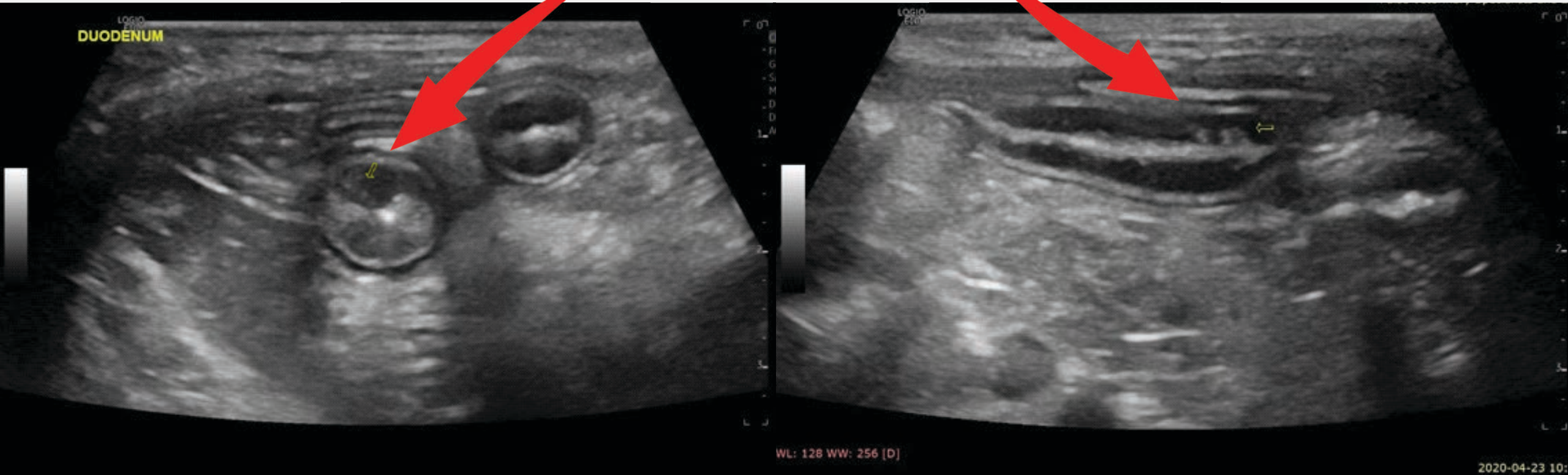
Blood Gas at Admission

Acid-base status		
pH	7.370	[7.360 - 7.470]
pCO ₂	35.6 mmHg	[33.0 - 52.0]
↓ SBE _C	-4.7 mmol/L	[-4.0 - 2.0]
cHCO ₃ ⁻ (P) _C	20.6 mmol/L	
Anion Gap _C	3.3 mmol/L	
↑ cCl ⁻	121 mmol/L	[106 - 120]
Metabolite values		
↓ cLac	0.5 mmol/L	[0.6 - 2.5]
cGlu	5.0 mmol/L	[4.1 - 6.6]
Electrolyte values		
cNa ⁺	145 mmol/L	[140 - 153]
↓ cK ⁺	3.6 mmol/L	[3.6 - 4.6]
↑ cCl ⁻	121 mmol/L	[106 - 120]
cCa ²⁺	1.20 mmol/L	[1.13 - 1.33]
cCa ²⁺ (7.4) _C	1.18 mmol/L	
ctHb	13.3 g/dL	
Hct _C	40.7 %	[37.0 - 57.0]



ABDOMINAL ULTRASOUND

Intestinal wall “striations”



TREATMENT

- Discussed endoscopy for biopsy collection
 - Not an ideal anesthetic candidate given the pleural effusion
 - Unlikely to change treatment in the short term (more on this later)
- Treatment:
 - Prednisone continued 2mg/kg/day
 - Changed metronidazole to Tylosin due to the lack of initial response
 - Hypoallergenic, low fat diet
 - Kangaroo low fat
 - 4 days in hospital, albumin gradually increased to 21 by day 4 and he was discharged

Why Endoscopy instead of exploratory Sx?



DO WE HAVE TO CONVINCe OWNERS?

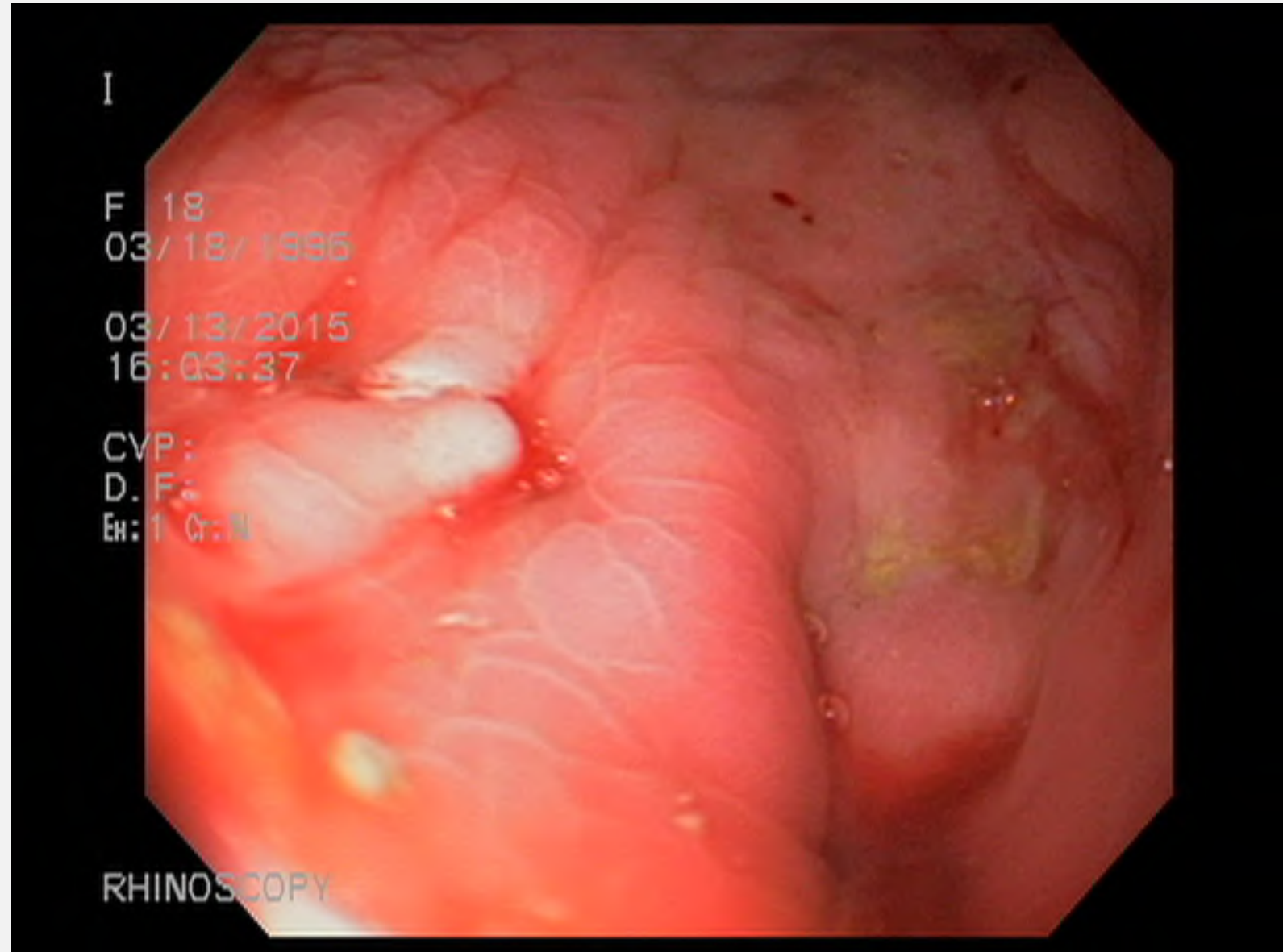
- By the time they come to me, they are usually motivated to go farther
- Why don't I just try meds to see what happens?
 - Is it better because of my drugs?
 - Is it not responding because I have the wrong dose? The wrong drug?
 - Not all cases have significant inflammation, so drugs may not help
 - So why put them at risk of adverse effects?
 - Adverse effects of drugs
 - No one likes a dog on pred! But, it is most effective drug a lot of the time
 - Clients run out of patience and money when things aren't going well

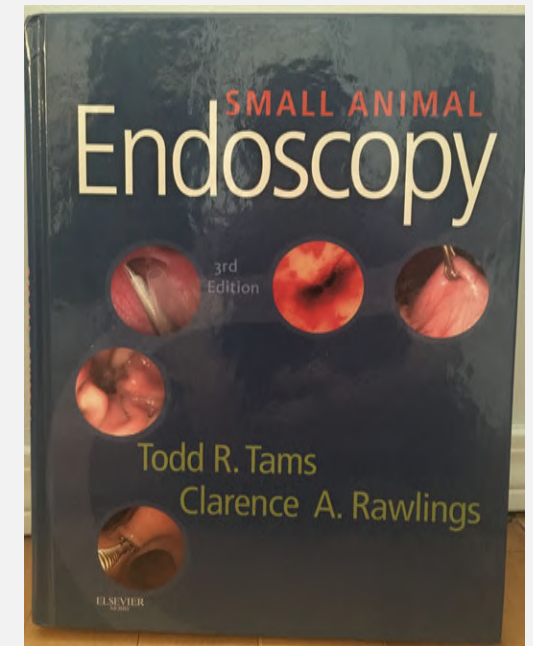
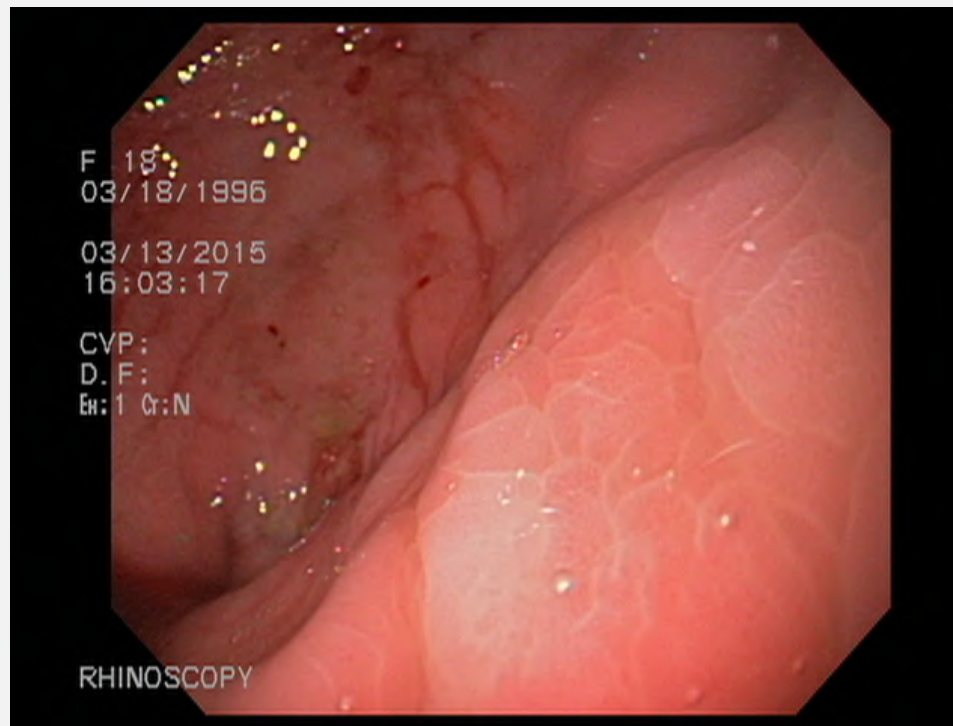
WHAT WOULD ENDOSCOPY
HAVE LOOKED LIKE?



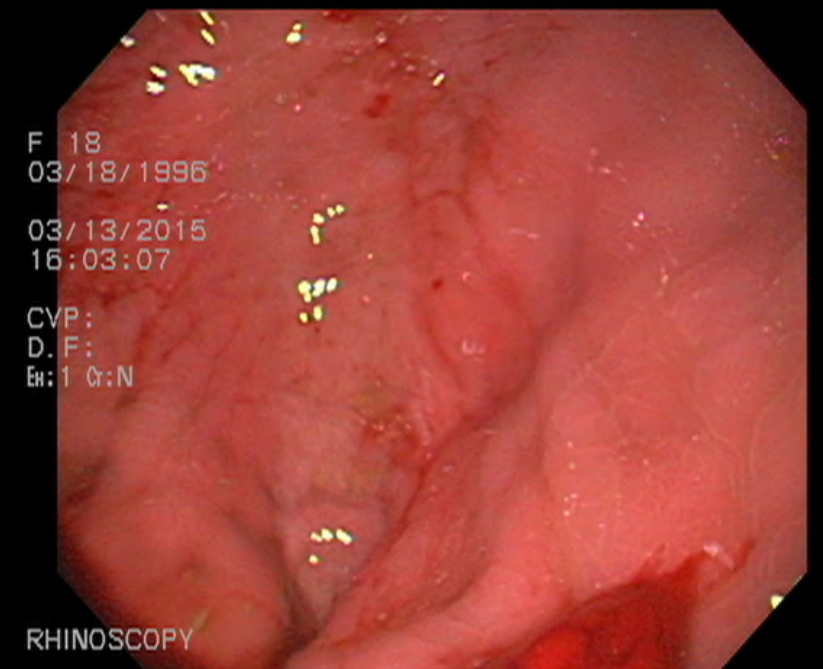
What does endoscopy look like?

- After we get through the LES
- Looking at Greater Curvature



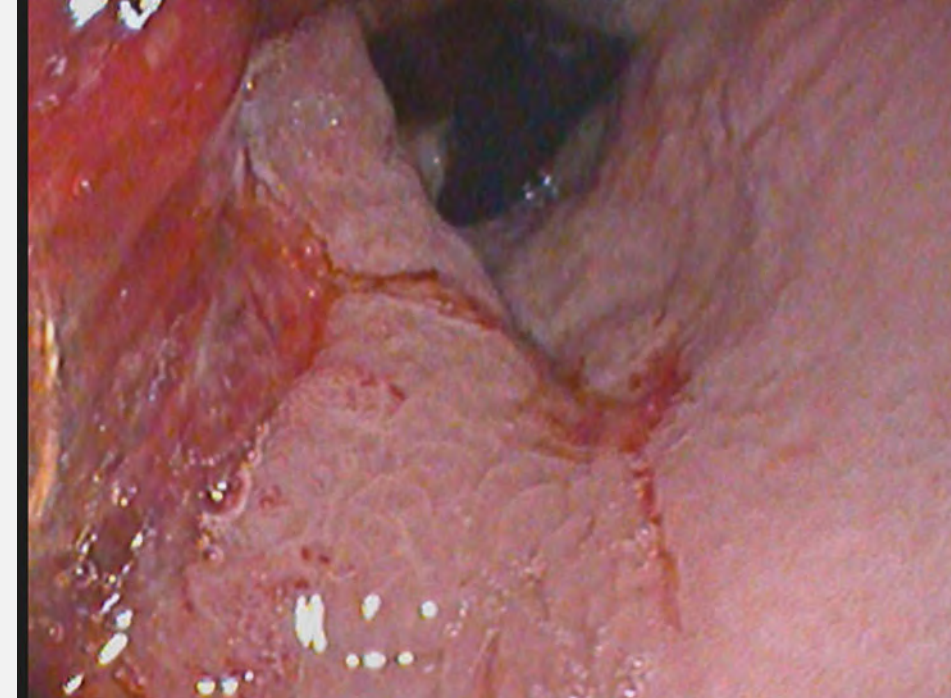


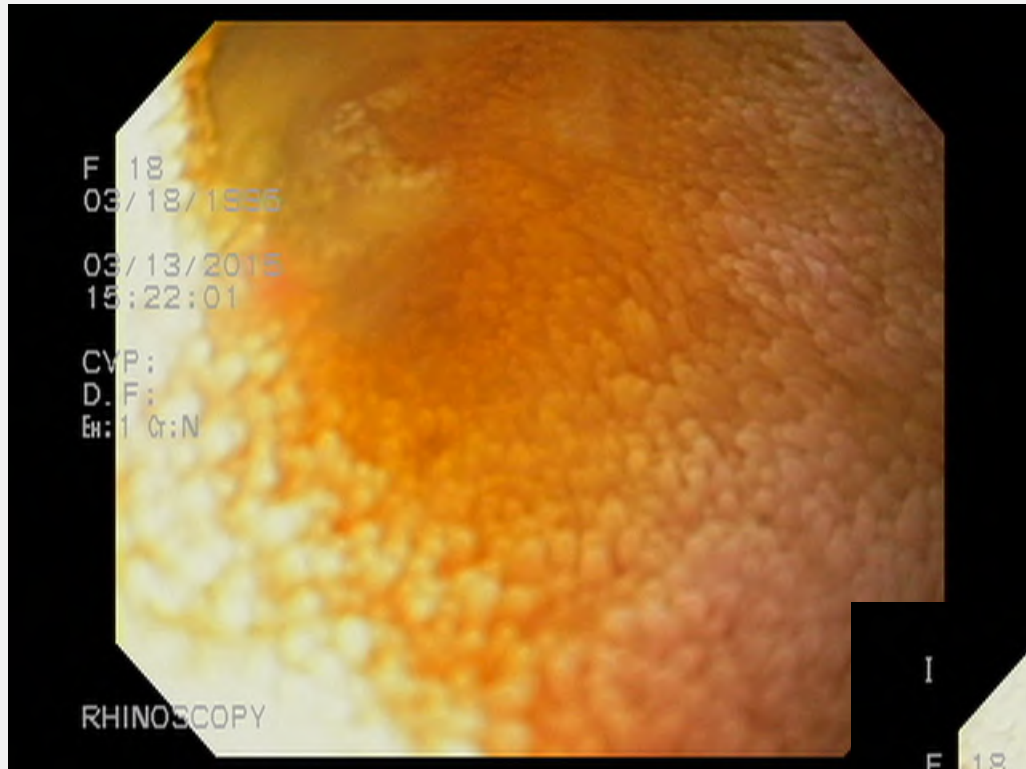
The scope is directed by sliding along the gastric wall, we only control where the tip looks, not where it goes!

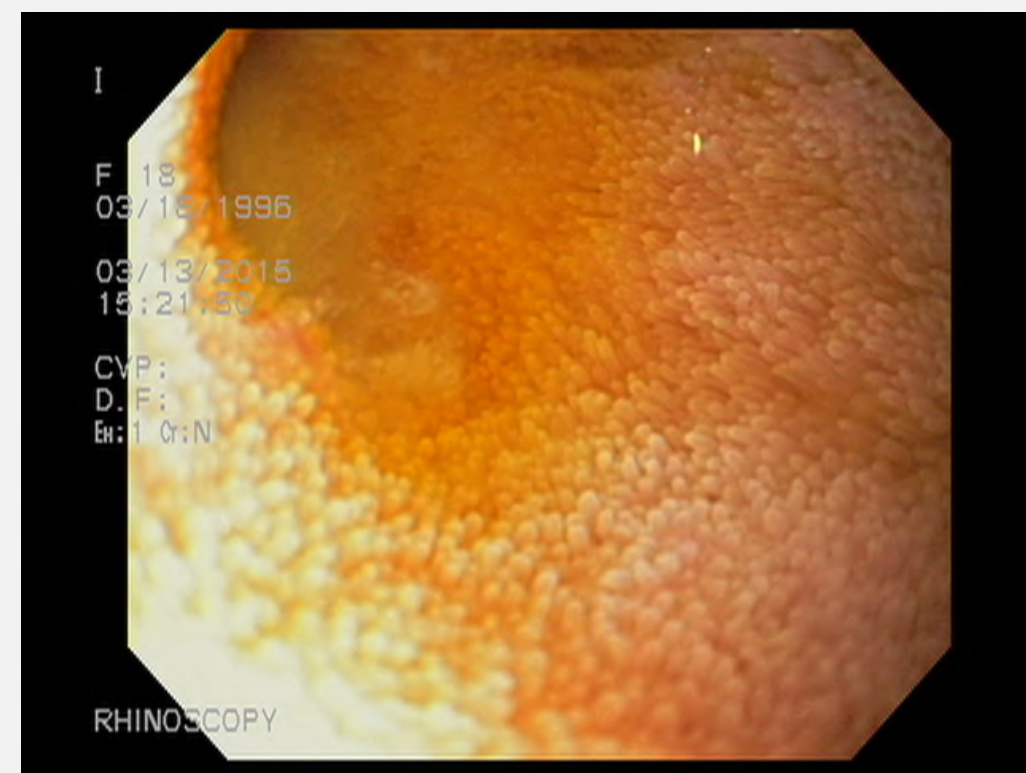
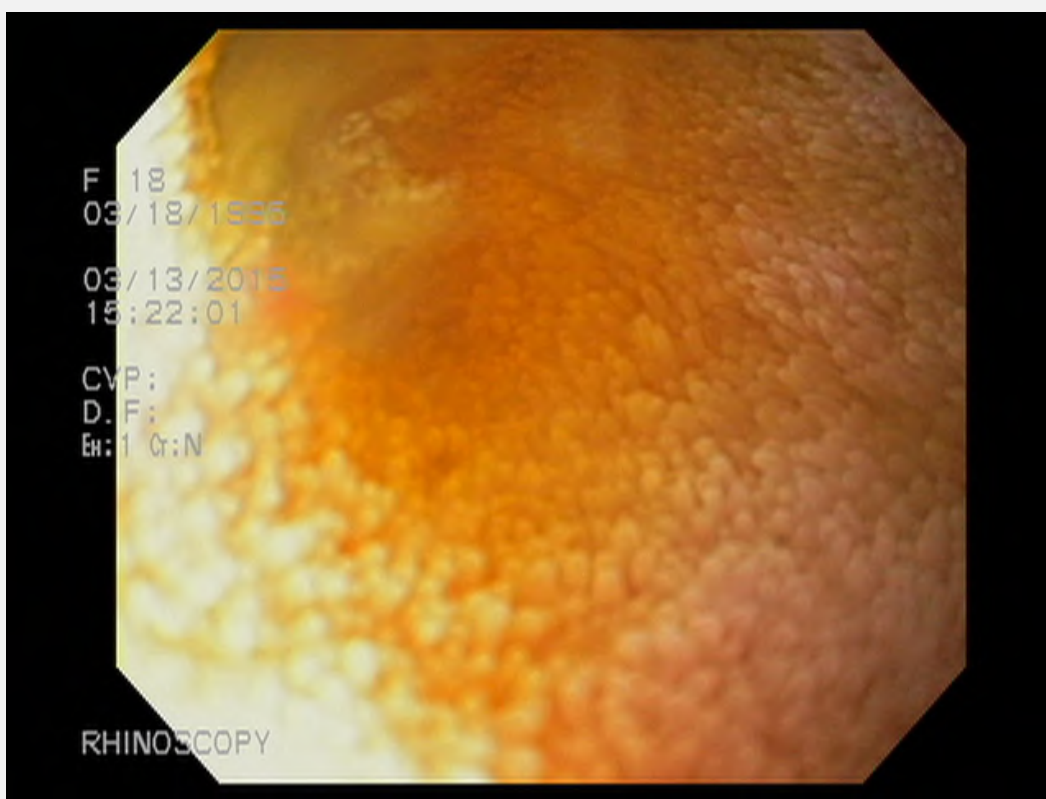


This is how we explore the stomach:

- Look for foreign bodies
- Find and biopsy masses
- Identify ulcers
- Collect biopsies ALWAYS!







Duodenum:

Top Left – villi in the proximal duodenum

Top Right – villi near the duodenal flexure

Bottom Right – view down the descending duodenum

F 18
03/18/1996

03/13/2015
16:03:25

CVP:
D.F:
Et: 1 Cr:N

RHINOSCOPY

We always biopsy 4 regions:

- 1) Antrum
- 2) Angularis incisura
- 3) Cardia
- 4) Greater Curvature

F 18
03/18/1996

03/13/2015
16:03:25

CVP:
D.F:
Et: 1 Cr:N

RHINOSCOPY

I

F 18
03/18/1996

03/13/2015
16:03:23

CVP:
D.F:
Et: 1 Cr:N

RHINOSCOPY

Biopsy forceps are quite small:

- Largest = 3.0mm
- Typical = 2.8mm
- Small = 2.0mm

Biopsy site



F 18
03/18/1996

03/13/2015
16:03:17

CVP:
D.F:
Et: 1 Cr:N

RHINOSCOPY

MICROSCOPIC DESCRIPTION:

Stomach: Eight fragments of gastric mucosa are available for assessment. These tissues are well preserved with minimal crush injury. There is attenuation of surface gastric epithelium on two biopsies with accompanying minimal lymphoplasmacytic inflammation noted within the superficial mucosa. Mucosal glands are tightly packed with no significant necrosis and mild fibrosis is noted on one biopsy.. There is no evidence of significant cellular atypia, mitotic activity or infectious agents noted on the sections examined.

Duodenum: Eight fragments of intestinal mucosa are available for assessment. These tissues are well preserved with minimal crush injury. The mucosa is distended by moderate infiltrates of lymphocytes and plasma cells. Surface villous epithelium is not attenuated however villi are mildly stunted. Lymphatics dilated (up to 50% of the longitudinal section of a villous was). Crypts frequently contain eosinophilic and cellular debris. There is no significant cellular atypia, mitotic activity or intraepithelial invasion.

MICROSCOPIC INTERPRETATION:

Stomach: Mild erosive lymphoplasmacytic gastritis with mild fibrosis

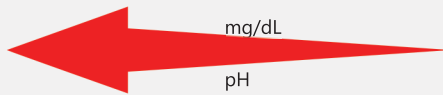
Duodenum: Moderate lymphoplasmacytic enteritis; lacteal dilation; protein-filled crypts

COMMENT:

There is no evidence of neoplasia or infectious agents. The lesions within the duodenum correlates with the clinical impression, of a protein losing enteropathy.

UA on admission

Test	Results	Ref. range	Unit
Collection method	Cystocentesis		
Color	Light yellow	Clear, Dark yellow, Pale yellow, Yellow	
Appearance	Clear		
Specific gravity (refractometer)	1.01	1.016 - 1.06	
Leukocytes	Negative		
Nitrite	Negative		
Urobilinogen	0		mg/dL
Protein	Negative		
pH	5		pH
Occult blood	Negative		
Ketones	Negative		
Bilirubin	Negative		
Glucose	normal		mg/dL
Sediment			
Amorphous crystals	None seen		/HPF
Amorphous phosphate crystals	None seen		/HPF
Amorphous urate crystals	None seen		/HPF
Bilirubin crystals	None seen		/HPF
Calcium oxalate monohydrate crystals	None seen		/HPF
Struvite crystals	None seen		/HPF
Other crystals (if any)	None seen		/HPF
Bacteria	None seen		/HPF
Leukocytes	None seen		/HPF
Erythrocytes	None seen		/HPF
Squamous epithelial cells	None seen		/HPF
Transitional epithelial cells	None seen		/HPF
Casts	None seen		/LPF
Oval fat bodies	None seen		/HPF



Why do we care about urine protein??

CBC on Admission

TEST	RESULT	REFERENCE VALUE	
RBC	6.04	5.65 - 8.87 x10 ¹² /L	
Hematocrit	0.394	0.373 - 0.617 L/L	
Hemoglobin	145	131 - 205 g/L	
MCV	65.2	61.6 - 73.5 fL	
MCH	24.0	21.2 - 25.9 pg	
MCHC	368	320 - 379 g/L	
RDW	15.3	13.6 - 21.7 %	
% Reticulocyte	1.4	%	
Reticulocytes	82.1	10.0 - 110.0 K/ μ L	
Reticulocyte Hemoglobin	26.9	22.3 - 29.6 pg	
WBC	29.81	5.05 - 16.76 x10⁹/L	H
% Neutrophils	89.5	%	
% Lymphocytes	6.8	%	
% Monocytes	3.4	%	
% Eosinophils	0.1	%	
% Basophils	0.2	%	
Neutrophils	26.68	2.95 - 11.64 x10⁹/L	H
Lymphocytes	2.04	1.05 - 5.10 x10 ⁹ /L	
Monocytes	1.01	0.16 - 1.12 x10 ⁹ /L	
Eosinophils	0.02	0.06 - 1.23 x10⁹/L	L
Basophils	0.06	0.00 - 0.10 x10 ⁹ /L	
Platelets	357	148 - 484 x10 ⁹ /L	
PDW	9.0	9.1 - 19.4 fL	L
MPV	10.2	8.7 - 13.2 fL	
Plateletcrit	0.36	0.14 - 0.46 %	

Chemistry

TEST	RESULT	REFERENCE VALUE	
Albumin	18	23 - 40 g/L	L 15

Chemistry

TEST	RESULT	REFERENCE VALUE	
Albumin	21	23 - 40 g/L	L 18 15

Follow up Albumin levels

PROTEIN LOSING ENTEROPATHY

This is not a single disease!

We have to identify the underlying cause in order to create a viable therapeutic plan!

Supportive therapies are helpful, but not the entire solution!



IBD



Lymphangiectasia or crypt disease



Breed Associated Diseases



Miscellaneous Diseases

TABLE 1 Causes of PLE in people and dogs

People	Dogs
1. Mucosal injury	
<i>a. Erosive</i>	
Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)	Inflammatory bowel diseases (lymphoplasmacytic, eosinophilic, granulomatous)
Infections: <i>Giardia, Clostridium, Campylobacter, Salmonella, rotavirus, Whipple's disease, intestinal tuberculosis</i>	Infections: <i>Parvovirus, Clostridium, Campylobacter, Salmonellosis, Histoplasmosis, Schistosomiasis (Heterobilharzia americana)</i>
Neoplasia	Neoplasia
Nonsteroidal enteropathy	Nonsteroidal enteropathy
<i>b. Non-Erosive</i>	
Menetrier's disease (hypertrophic gastritis)	Diet-induced enteropathy
Eosinophilic gastritis	Immunoproliferative enteropathy
Celiac disease	Hypoadrenocorticism
Lactose or other food intolerance	Intestinal crypt disease
Systemic lupus erythematosus	
Intestinal crypt disease	

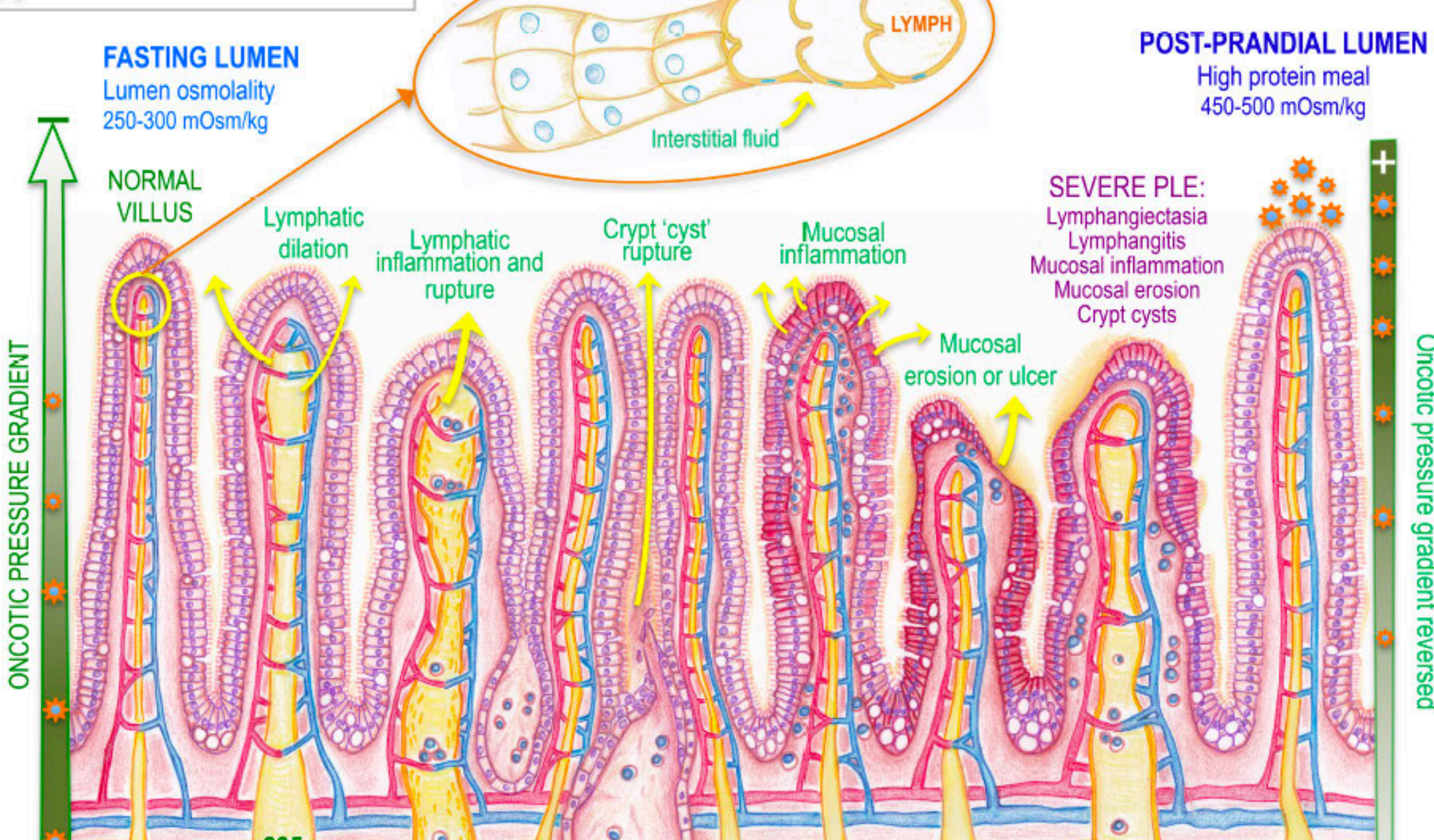
REVIEW**Comparative pathophysiology and management of protein-losing enteropathy**Melanie D. Craven¹ | Robert J. Washabau²**2. Infectious**

Lymphatic filariasis	Lymphatic filariasis (RARE)
	Hookworms
	<i>Strongyloides stercoralis</i>

3. Lymphatic disease

Idiopathic primary IL (Waldmann's disease)	Idiopathic primary IL
Secondary IL: Crohn's disease, neoplasia sarcoidosis, congestive heart failure, restrictive pericarditis	Secondary IL: IBD, neoplasia, lymphatic infections, right-sided congestive cardiac failure
Fontan surgery	Lymphangitis (granulomatous/inflammatory)
Genetic: Lymphodysplasia (Hennekam's syndrome)	
Lymphangitis	

Abbreviations: IBD, inflammatory bowel disease; IL, intestinal lymphangiectasia.



LYMPHANGIECTASIA

- Dilation of lacteals, crypts and lymphatic ducts
 - Results in fat malabsorption, leakage of protein and alteration of osmotic gradients to cause fluid shifts
- Can be primary intestinal lymphangiectasia (IL) or secondary to other disease
 - Primary IL occurs in humans, but it is unclear if this is truly the same thing in dogs
 - Most often associated with lymphoplasmacytic enteritis (IBD)
 - Can occur secondary to blocked lymphatics
 - Neoplasia
 - Granulomatous disease

LYMPHANGIECTASIA

- Historical Signs:
 - Vomiting, diarrhea, weight loss,
 - PU/PD
 - Ascites
- Clinical Signs:
 - Muscle wasting/cachexia
 - Abdominal distention – ascites
 - Abdominal discomfort
 - Tachypnea (pleural effusion)



BREED FREQUENCIES FOR CANINE LYMPHANGIECTASIA

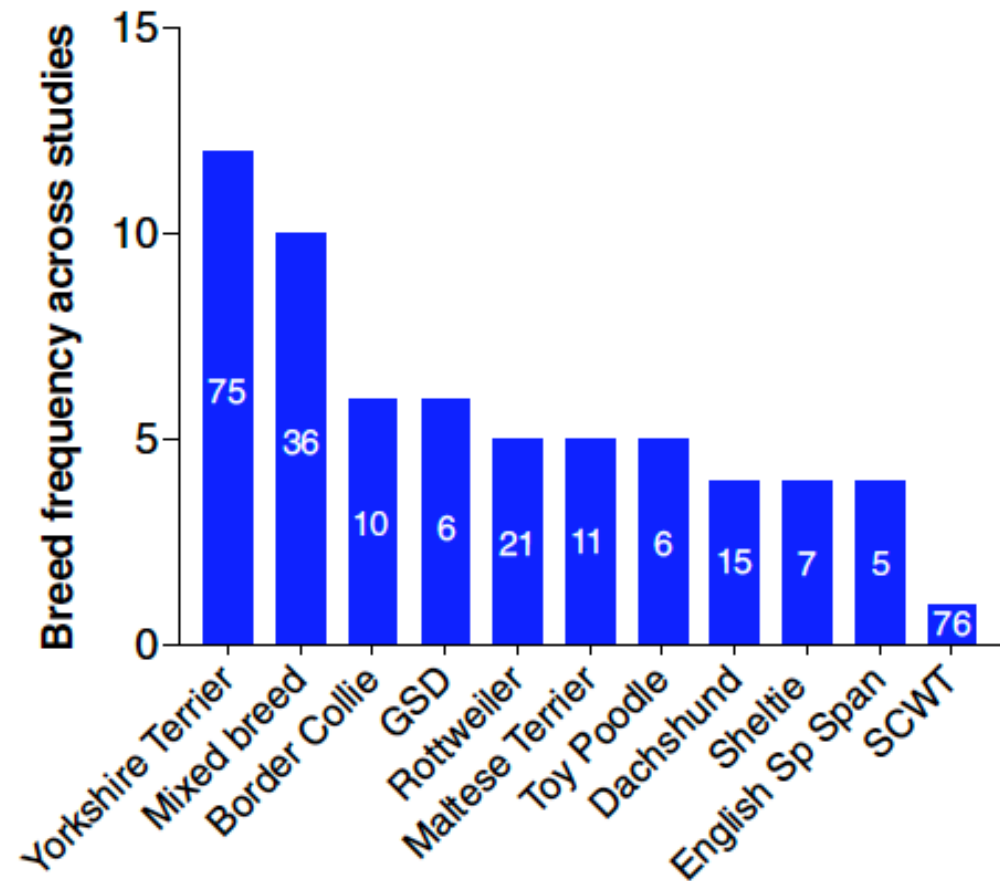


FIGURE 4 Breed frequencies represented across canine PLE publications; numbers on bars indicate the number of dogs within the breed.^{12,13,49–69} PLE, protein-losing enteropathy

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Journal of Veterinary Internal Medicine



REVIEW

Comparative pathophysiology and management of protein-losing enteropathy

Melanie D. Craven¹ | Robert J. Washabau²

PLE PROGNOSTIC FACTORS

- 3 year survival rate =70%
- PLE dogs with hypercoagulability have a 66% mortality rate at 5 months
- Normalization of albumin within 50 days associated with longer survival
 - Also normalization of CIBDAI or CCECAI
 - Chronic enteropathy scoring systems
 - Several studies suggest low ALB is a poor prognostic indicator
 - But they ALL have it!
- Elevated BUN?
 - May be a worse sign – possible indication of disease severity, not sure yet
- GI lymphoma as a cause of your PLE is worse

CRYPT DISEASE

- Dilation of intestinal crypts with mucous, sloughed epithelial cells and sometimes inflammatory cells
- Not associated with histologic signs of IBD or lymphangiectasia
- May have isolated or patchy distribution of lesions
- Similar to ulcerative colitis in people (kind of...)
- Yorkshire Terriers the most common
 - Also Rottweilers
- Outcome can be quite poor – 58% died within 3 months in one study
 - Though some did survive past 2-3 years



QUESTIONS?

Thank you all for listening and to the SBVC for inviting me to speak

IMMUNOSUPPRESSIVE TREATMENT

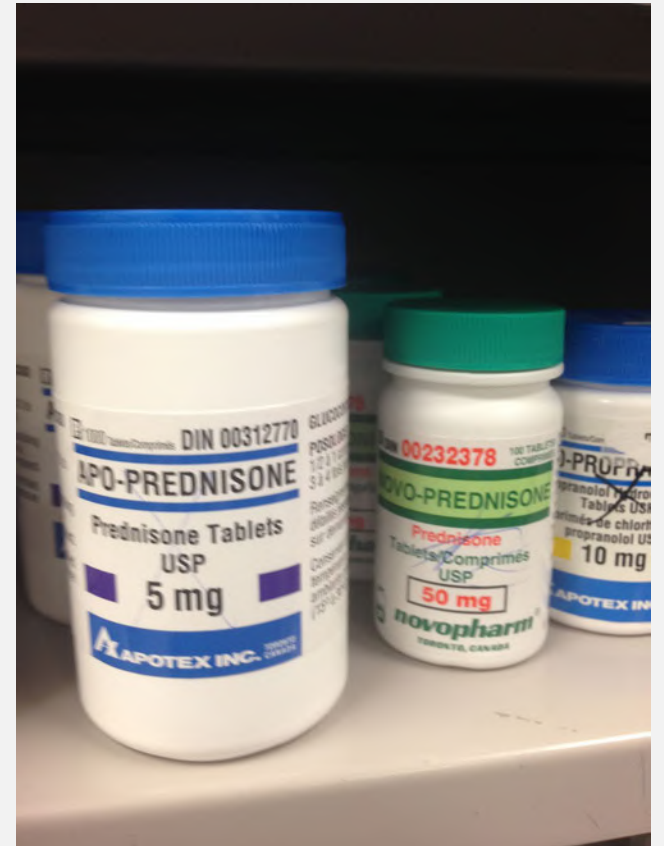
Which drugs are useful and how do we use them?

IMMUNOSUPPRESSION AND GI DISEASE

- When do we take this plunge?
 - Ideally, based on biopsies – realistically, we do this when we have reached the end of the client's willingness to work up the case
- Immunosuppression doesn't usually work alone
 - Not a replacement for dietary therapy in most cases
 - Dose is IMPORTANT
 - If you're going to do it, do it right!
- Goal is to control signs – This is not a cure!
 - There will be relapses periodically
 - Would like to reach the lowest possible dose of drug that controls clinical signs

GLUCOCORTICOIDS

- Prednisone/prednisolone
 - Cats get prednisolone!
- Budesonide
 - Supposedly poorly absorbed so has more local effects
 - Does still affect the HPA though, so some is absorbed
 - Maybe fewer adverse effects
 - I like it for large bowel disease



OUR HERO: PREDNISONE

The White Knight

- Rapid impairment of macrophage mediated destruction
- Decreased immunoglobulin production
 - Key feature for us with autoimmune disease
- Altered T lymphocyte generation and function

The Dark Knight

- PU/PD
- Polyphagia
- Muscle wasting/myopathy
- Collagen weakness
 - Ligament ruptures?
- GI ulceration
- Dermatological changes
 - Pot belly, calcinosis cutis
- Behavioral changes

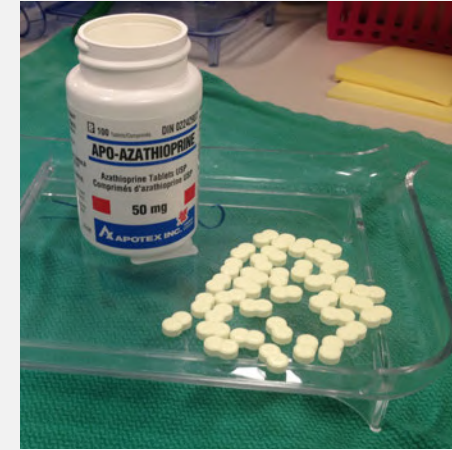
PREDNISONONE

- Immunosuppressive dose = **2mg/kg/day**
 - More does **NOT** get better immune suppression!
 - More does get more adverse effects
 - CATS – 3-4mg/kg/day
- Dexamethasone can be used early, when injectable drugs are required
 - 0.25mg/kg/day (roughly 8-10x more potent than prednisone)
- Lots of alternative dosing strategies:
 - Body surface area, extended intervals, shortened duration, pulse therapy
 - None proven to provide the required effect with fewer adverse effects



AZATHIOPRINE

- Purine analogue antimetabolite
 - Inhibits RNA, DNA & protein synthesis resulting in decreased lymphocyte proliferation
 - Effective in 11 to 14 days (NOT a fast drug)
- Immunosuppressive dose = 2mg/kg/day
 - For how long?
 - I use it daily until I wean my prednisone to a tolerable dose
 - Others decrease after 7-14 days to EOD



The Effects of Prednisone and Azathioprine on Circulating Immunoglobulin Levels and Lymphocyte Subpopulations in Normal Dogs

Nancy E. Rinkardt, Stephen A. Kruth, and Azad Kaushik

Prednisone decreased circulating antibodies, but azathioprine did not. However, in people Aza does. This is where the delayed effects of azathioprine come from.

AZATHIOPRINE ADVERSE EFFECTS

- Hepatotoxicity:
 - Idiosyncratic reaction, usually within first 4 wks
 - May include rash, fever, joint/muscle pain
 - Dose dependent toxicity:
 - Elevation of ALT >2x reference interval (average of 8-9x normal in dogs with a rxn)
 - Occurred in 15% of dogs in study (5 of 34)
 - Usually occurs within 2-3 weeks in dogs, stabilized or resolves when drug is stopped
 - GSDs overrepresented

Much less common than we all fear!

Incidence, Timing, and Risk Factors of Azathioprine Hepatotoxicosis in Dogs

K. Wallisch and L.A. Trepanier

- Bone marrow toxicosis (reported at 3-16 weeks)
 - Thrombocytopenia or neutropenia
 - Occurred in 8% of dogs (4 of 48)
 - 1.5 to 7 months after starting (median 53 days)
- GI signs and acute pancreatitis have also been reported
- Monitoring:
 - Have to follow CBC and hepatic enzymes
 - Especially for first few months



NO AZATHIOPRINE IN CATS!!!

Cats are low in thiopurine methyltransferase and can't metabolize it resulting in higher rate of adverse effects

CYCLOSPORINE



- Calcineurin inhibitor that prevents production of IL-2, which is necessary for activation of T lymphocytes
- Immunosuppressive dose = 5mg/kg BID
 - Accumulates in skin, so for derm diseases once daily dosing is sufficient (hence the label)
 - For non derm disease, needs to start BID – levels can be monitored through Mississippi State U
- Adverse Effects:
 - Gastrointestinal signs – about 25% of dogs – less frequent if you store it in the freezer!
 - Gingival hyperplasia
 - Papilloma-like skin lesions, hair loss
 - Secondary infections (especially in combination with other immunosuppressives)

CHLORAMBUCIL

Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007–2010)

Julien R. S. Dandrieux, Dr med vet, DACVIM; Peter-John M. Noble, BVM&S, PhD;
Timothy J. Scase, BVM&S, PhD, DACVP; Peter J. Cripps, BVSc, PhD; Alexander J. German, BVSc, PhD

- Alkylating agent
- Used as an alternative to azathioprine in cats
 - Often combined with prednisolone for treatment of small cell lymphoma in cats
 - Very well tolerated!
- Retrospective comparison to pred/azathioprine combo to treat PLE in dogs suggests that pred/chloambucil may provide quicker and more durable remission
- Dosing:
 - 0.1-0.2mg/kg PO once daily x 7-14 days, then every other day after that
 - Another reason why the cat people love it!
- Adverse effects?
 - GI signs, neutropenia (both uncommon)
- Often need to compound it to get the proper size
 - 2mg tablet
- Chemotherapy drug
 - Handling requirements
 - Owner considerations
- Cost can vary

NEW KIDS ON THE BLOCK

Leflunomide

- Pyrimidine synthesis inhibitor
- Promising in refractory cases
- Adverse Effects:
 - Gastrointestinal signs

DNA synthesis inhibitors – decrease lymphocyte and antibody production

Mycophenolate mofetil

- Purine synthesis inhibitor
 - Similar to azathioprine
 - So can't use together!
- Used to help get refractory cases under control
 - Discontinued after remission
- Adverse Effects:
 - Gastrointestinal signs

MONOTHERAPY?

- Many recommend treatment with prednisone alone unless the patient fails to respond
 - Adverse effects?
 - Maybe on a higher dose for longer or slower to taper medications
 - Consequences of failure to respond?
 - Owners run out of patience and money
- I start medium to large breed dogs on dual therapy from the outset
 - The muscle wasting, weakness, and PU/PD/polyphagia is just too much for a lot of people
 - Also use dual therapy in severe cases
 - Severe PLE – remember, the faster they improve, the better their long term outcome (maybe!)

TEAMWORK!

Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007–2010)

Julien R. S. Dandrieux, Dr med vet, DACVIM; Peter-John M. Noble, BVM&S, PhD;
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- Benefits of both
 - Immune suppression by multiple mechanisms of action
 - May promote a faster response
- Lets us manage adverse effects better
 - Combining a second immunosuppressive with prednisone may allow us to taper e a bit more rapidly without risk of relapse
 - Helps get rid of adverse effects that owners care about!
- Risks?
 - Greater immunosuppression = greater risk of secondary infection
 - Increased cost
 - Increased monitoring requirements

SINGLE AGENT IMMUNOSUPPRESSION PLAN

Drug	Dose	Duration	Comments
Prednisone	2mg/kg/day	2-3 weeks	May need to consider additional drug if no response
Prednisone	1.5mg/kg/day	2-3 weeks	
Prednisone	1mg/kg/day	2-3 weeks	
Prednisone	0.5mg/kg/day	2-3 weeks	
Prednisone	0.5mg/kg EOD	4-6 Weeks	Moving to EOD is a major point of relapse
Prednisone	Discontinue	Stopping is a major point of relapse	May need to move to every 2 nd day before stopping

DOS AND DON'TS OF TAPERING

- This is NOT a race
- Taper based on monitoring
 - Both before AND after
- Taper only 1 thing at a time
 - One immunosuppressive, one antibiotic, etc...
- Monitoring:
 - What are we monitoring?
 - What was abnormal
 - Albumin, total protein
 - Clinical signs
 - Hematology (IMHA for example)
 - Adverse effects
 - Depends on drugs i.e. azathioprine

Drug Combination	Dose	Duration	Comments
1) Prednisone 2) Azathioprine	1) 2 mg/kg/day 2) 2 mg/kg/day	2-3 weeks	Monitor for drug reaction prior to start and at 2-3 weeks
1) Prednisone 2) Azathioprine	1) 1.5 mg/kg/day 2) 2mg/kg/day	2-3 weeks	
1) Prednisone 2) Azathioprine	1) 1 mg/kg/day 2) 2 mg/kg/day	2-3 weeks	Monitor for drug reaction
1) Prednisone 2) Azathioprine	1) 0.5 mg/kg/day 2) 2 mg/kg/day	2-3 weeks	
1) Prednisone 2) Azathioprine	1) 0.5 mg/kg/day 2) 2 mg/kg EOD	2-3 weeks	Monitor for drug reaction
1) Prednisone 2) Azathioprine	1) 0.5 mg/kg EOD 2) 2 mg/kg/ EOD	4-6 weeks	
1) Prednisone 2) Azathioprine	1) 0.5 mg/kg EOD 2) Discontinue	4-6 weeks	Monitor for drug reaction
1) Prednisone	1) Discontinue	Recheck 2-3 weeks	Monitor for relapse

IMPORTANT NOTES FOR OWNERS

- This is NOT a cure!
 - There will be relapses in the future, just like in people with chronic GI disease
- Our goal is to get patients off of all medications, but that happens in <50% of cases
- Adverse Effects!
 - You *MUST* tell people about these things – they can be overwhelming to many
- No changes or stopping medications on their own!
 - Dogs (and maybe cats) become dependent on exogenous glucocorticoids as a result of adrenal suppression. Steroids must be tapered after they have been on them for several weeks
- Drugs are not a replacement for diet/lifestyle changes!

NUTRITIONAL MANAGEMENT OF PLE

- Two major goals:
 - 1) Replenish proteins and rebuild muscle mass
 - 2) Provide energy while nondigestible fats
- Highly digestible
 - Meaning 88-90% digestibility
 - >95% for carbohydrates and fats
 - Contain more than 20-25% protein (on a dry matter basis)
 - May need to be a novel protein if there is an IBD component on histo
 - Less than 10-15% fat
 - May need to be *much* lower if lymphangiectasia present
- Less than 5% insoluble fibre

This is a great time to remind you of our sponsor, Hill's

I say this because food companies can be a great resource to help you select a diet

Comparisons of Selected Highly Digestible, Hypoallergenic, and Hydrolyzed Diets Used in the Management of Protein-Losing Enteropathies in Dogs

	% Protein Dry*	% Protein Can*	% Fat Dry*	% Fat Can*	Protein Source
Royal Canin Digestive Low Fat	20.5	16.7	5.0	3.4	Chicken, pork
Hill's Prescription Diets i/d	26.5	27.8	14.1	14.3	Chicken, egg
Hill's Prescription Diets i/d low fat	25.9	25.1	7.4	8.5	Chicken/turkey, pork
Purina Veterinary Diets EN	23	—	10.5	—	Chicken
P&G Iams Low Residue	24.6	33	10.7	18.9	Chicken
Royal Canin Hypoallergenic HP	19	—	17	—	Soy protein isolate
Hill's Prescription Diet z/d	19	19.5	13.9	13.9	Chicken
Purina Veterinary Diets HA	18	—	8.0	—	Soy protein isolate
Royal Canin Hypoallergenic PD	19	17.7	10.5	16.7	Duck
Royal Canin Hypoallergenic PV	19.5	16.7	10	11.7	Venison
Royal Canin Hypoallergenic PR	19.5	18.4	10.5	13.3	Rabbit
Hill's Prescription Diet d/d duck	18	17.4	16.7	16.6	Duck
Hill's Prescription Diet d/d salmon	18.4	18.9	15.5	14.8	Salmon
Purina Veterinary Diets DRM	24	—	12	—	Salmon/trout

*Dry matter basis.

PLE DIETARY MANAGEMENT

- An Ultra Low-Fat Diet was found to result in:
 - Improvement in clinical activity index
 - Decrease in prednisone dose
 - Clinical response in dogs that did not initially respond to prednisone alone
- Utilize nutrition services to create a balanced ULF diet

J Vet Intern Med 2014;28:809–817

The Clinical Efficacy of Dietary Fat Restriction in Treatment of Dogs with Intestinal Lymphangiectasia

H. Okanishi, R. Yoshioka, Y. Kagawa, and T. Watari

Background: Intestinal lymphangiectasia (IL), a type of protein-losing enteropathy (PLE), is a dilatation of lymphatic vessels within the gastrointestinal tract. Dietary fat restriction previously has been proposed as an effective treatment for dogs with PLE, but limited objective clinical data are available on the efficacy of this treatment.

Hypothesis/Objectives: To investigate the clinical efficacy of dietary fat restriction in dogs with IL that were unresponsive to prednisolone treatment or showed relapse of clinical signs and hypoalbuminemia when the prednisolone dosage was decreased.

Animals: Twenty-four dogs with IL.

Methods: Retrospective study. Body weight, clinical activity score, and hematologic and biochemical variables were compared before and 1 and 2 months after treatment. Furthermore, the data were compared between the group fed only an ultra low-fat (ULF) diet and the group fed ULF and a low-fat (LF) diet.

Results: Nineteen of 24 (79%) dogs responded satisfactorily to dietary fat restriction, and the prednisolone dosage could be decreased. Clinical activity score was significantly decreased after dietary treatment compared with before treatment. In addition, albumin (ALB), total protein (TP), and blood urea nitrogen (BUN) concentration were significantly increased after dietary fat restriction. At 2 months posttreatment, the ALB concentrations in the ULF group were significantly higher than that of the ULF + LF group.

Conclusions and Clinical Importance: Dietary fat restriction appears to be an effective treatment in dogs with IL that are unresponsive to prednisolone treatment or that have recurrent clinical signs and hypoalbuminemia when the dosage of prednisolone is decreased.

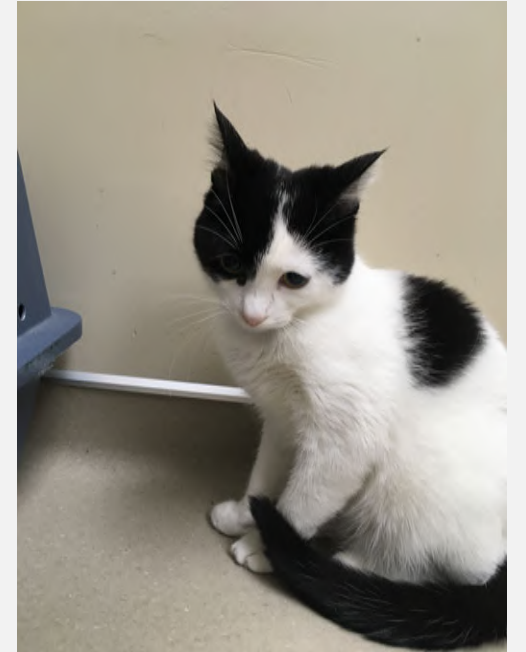
Key words: Canine; Inflammatory bowel disease; Protein-losing enteropathy.

PLE AND COAGULATION

- Losing protein means you are going to lose some important stuff!
- Antithrombin deficiency (along with other factors) is a major concern in PLE
- Because there is no effective clot removal therapy in dogs/cats, prevention is key
- Clopidogrel (Plavix) 2-4 mg/kg PO once daily
 - 75mg tablet, so dosing is often based on what you can reasonably get
- Aspirin
 - MUCH debate on what dose is actually antithrombotic
 - We used to say 1-2mg/kg/day (dog)
 - Now some suggest 10mg/kg/day
 - Requires GI protectant therapy because can be ulcerogenic at this dose

ROXY

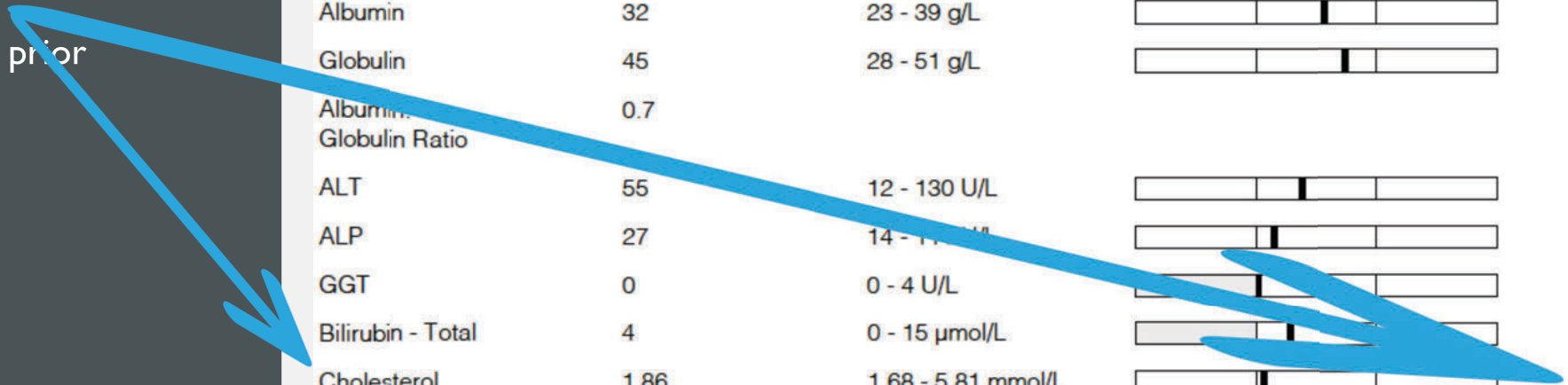
- 8-year-old FS DSH
- Initially evaluated 1.5 months prior for vomiting of several weeks' duration
 - AUS noted support for pancreatitis (hypoechoic pancreas)
 - Managed supportively with fluids, buprenorphine and Cerenia
 - Returned home and began to eat normally after a few days
- 1 week prior to returning she had another episode of vomiting
- Historical episodes of constipation
 - Managed well at home on a high fibre diet and PEG powder (no recent episodes)
- Physical Exam – quite unremarkable
 - Slightly overweight (7kgs)
 - Grade 2/6 systolic murmur, left parasternal PMI



ROXY - DIAGNOSTICS

- CBC – completely normal
- Biochemistry – Normal
 - Low normal cholesterol
 - Actually low the month prior
- Urinalysis
 - 1.049 USG
 - Quiet sediment
- FeLV/FIV negative

TEST	RESULT	REFERENCE VALUE		
Glucose	6.73	3.95 - 8.84 mmol/L		6.87
Creatinine	129	71 - 212 µmol/L		145
Urea (BUN)	5.8	5.7 - 12.9 mmol/L		5.2
BUN: Creatinine Ratio	11			9
Phosphorus	1.36	1.00 - 2.42 mmol/L		1.27
Calcium	2.29	1.95 - 2.83 mmol/L		2.27
Sodium	162	150 - 165 mmol/L		155
Potassium	3.8	3.5 - 5.8 mmol/L		3.5
Na: K Ratio	43			44
Chloride	122	112 - 129 mmol/L		122
Total Protein	77	57 - 89 g/L		82
Albumin	32	23 - 39 g/L		34
Globulin	45	28 - 51 g/L		48
Albumin: Globulin Ratio	0.7			0.7
ALT	55	12 - 130 U/L		59
ALP	27	14 - 114 U/L		38
GGT	0	0 - 4 U/L		0
Bilirubin - Total	4	0 - 15 µmol/L		5
Cholesterol	1.86	1.68 - 5.81 mmol/L		1.25
Osmolality	321	mmol/kg		307




ENDOSCOPY & INITIAL RESULTS

- Upper GI endoscopy – Gross appearance
 - Marked mucosal thickening of the stomach and duodenum
 - No mass lesions or ulcerative changes

MICROSCOPIC DESCRIPTION :


Duodenum : The lamina propria diffusely contains marked numbers of small lymphocytes. There is moderately to sometimes markedly increased intraepithelial lymphocytes within the superficial epithelium and the crypt epithelium.

Stomach : The lamina propria is mildly edematous and has mild numbers of lymphocytes and plasma cells. Few spiral shaped bacteria are present on the surface and within some gastric pits.



MICROSCOPIC INTERPRETATION :

Atypical round cell proliferation with increased intraepithelial lymphocytes (see comments)



COMMENT :

This is a very severe small lymphocyte infiltrate. Changes could be consistent with a severe exuberant inflammatory proliferation but the major differential is small cell lymphoma. These two processes may be very difficult to differentiate by biopsy alone; definitive interpretation often cannot be made on biopsy samples of limited size and depth such as these. Clinical differentiation may require evaluation of clinical progression and response to therapy. The distinction between severe lymphocytic inflammatory disease and insidious or emerging small cell lymphoma is not clear and these may actually represent a continuum of dysregulation of lymphocyte proliferation.

IBD VS. SMALL CELL GASTROINTESTINAL LYMPHOMA

- Is there a difference?
 - Constant debate!
- Chronic inflammation is linked to GI neoplasia in animal models and people
 - Bacterial component to trigger IBD?





DOI: 10.1111/jvim.15291

Journal of Veterinary Internal Medicine

ACVIM
American College of
Veterinary Internal Medicine

STANDARD ARTICLE

Relationship of the mucosal microbiota to gastrointestinal inflammation and small cell intestinal lymphoma in cats

Kayode Garraway¹  | Chad M. Johannes² | Angela Bryan³ | John Peauroi⁴ | Giacomo Rossi⁵ | Min Zhang⁶ | Chong Wang⁷ | Karin Allenspach⁸ | Albert E. Jergens⁹ 

progression and response to therapy. The distinction between severe lymphocytic inflammatory disease and insidious or emerging small cell lymphoma is not clear and these may actually represent a continuum of dysregulation of lymphocyte proliferation.



HOW DO WE DIFFERENTIATE?

- How about with ultrasound?
 - Noninvasive
 - Somewhat cost effective...
- We can tell IBD/SCLSA apart from normal/healthy cats
 - But not from each other

Interesting side note



Published in final edited form as:

J Feline Med Surg. 2014 February ; 16(2): 89–98. doi:10.1177/1098612X13498596.

Ultrasonographic thickening of the muscularis propria in feline small intestinal small cell T-cell lymphoma and inflammatory bowel disease

Lise A Daniaux¹, Michele P Laurenson¹, Stanley L Marks², Peter F Moore³, Sandra L Taylor⁴, Rachel X Chen⁴, and Allison L Zwingenberger⁵

Gastrointestinal lymphoma is the most common form of lymphoma in the cat. More recently, an ultrasonographic pattern associated with feline small cell T-cell gastrointestinal lymphoma has been recognized as a diffuse thickening of the muscularis propria of the small intestine. This

disease (IBD) and 19 healthy cats. We found a significantly increased thickness of the muscularis propria in cats with lymphoma and IBD compared with healthy cats. The mean thickness of the muscularis propria in cats with lymphoma or IBD was twice the thickness than that of healthy

No cats in the present study had lymphocytic infiltrates in the muscularis layer of the intestinal segments, indicating that the presence of lymphoma cells in the muscularis propria cannot explain the increased thickness of this layer. No cats in the IBD group had disease deeper than the mucosal layer. A relationship between the thickness of the muscularis layer and the extent of the neoplastic lymphocytic infiltration has been described previously,⁷ with the muscularis thickening giving increased odds of transmural disease to the depth of the submucosa. This is supported by the current results in which the majority of bowel

HOW SHOULD WE GET SAMPLES?

- Endoscopy
 - Less invasive than surgery
 - Less risk of perforation/dehiscence
 - Less costly than surgery
 - Only mucosal biopsies, and only from duodenum, can reach ileum if also do colonoscopy
- Surgery
 - Full thickness samples
 - Multiple areas of the SI – duodenum, jejunum, ileum
 - Expensive
 - Risk of dehiscence – this is not healthy tissue we are putting back together



Surgeons should not touch flexible endoscopes...

SO HOW DO WE REALLY TELL?

- PCR for Antigen Receptor Rearrangement
 - Normal lymphocytes are widely varied
 - For all the antigens out in the world
 - Neoplastic lymphocytes are just copies of themselves
 - So surface receptors are all alike

BUT....there can be false positives...and negatives...


Received: 31 January 2019 | Revised: 14 May 2019 | Accepted: 12 June 2019

DOI: 10.1111/vcp.12767

ORIGINAL ARTICLE

Veterinary Clinical Pathology
An International Journal of Laboratory Medicine WILEY

Assessment of immunoglobulin heavy chain, immunoglobulin light chain, and T-cell receptor clonality testing in the diagnosis of feline lymphoid neoplasia

Emily D. Rout  | Robert C. Burnett | Janna A. Yoshimoto | Paul R. Avery | Anne C. Avery

Results: Using four immunoglobulin primer sets (IGH-VDJ, IGH-DJ, Kde, and IGL), clonal immunoglobulin rearrangements were detected in 87% (33/38) of the presumed B-cell neoplasms. The IGH-VDJ reaction alone only detected clonality in 50% (19/38) of these cases. TRG rearrangements were clonal in 97% (29/30) of the T-cell leukemia cases. All negative control samples had polyclonal immunoglobulin and TRG rearrangements.

Conclusions: The PARR assay developed in this study is useful for assessing clonality in feline lymphoid neoplasms. Clonality assessment of incomplete IGH-DJ, Kde, and IGL rearrangements helped identify clonal B-cell neoplasms not detected with complete IGH-VDJ PARR alone.

EXTENDED RESULTS

- We did request PARR assessment:

COMMENT:

Clonality testing targeting the feline T cell receptor gamma (TRG) locus revealed a clonal rearrangement in a polyclonal background. In conjunction with the clinical and histologic findings, these results are consistent with a diagnosis of T cell lymphoma. The confidence in this diagnosis is high.

CLONALITY TESTING RESULTS

DIAGNOSIS:

Duodenum: Lymphoma, enteropathy-associated type II

Clonality PCR testing is referred out to the Pathobiology Lab (Animal Health Laboratory, University of Guelph).

TREATMENT OF GI SCLSA

- My preferred combination:
- Prednisolone 2mg/kg/day
- Chlorambucil
 - I tend to do 2 mg EOD
 - Can do q2 weeks as described here
- Once clinical signs controlled, I begin to taper the prednisone
 - Every 2-3 weeks until I reach 1 mg/kg/day

Published in final edited form as:

J Am Anim Hosp Assoc. 2010 ; 46(6): 413–417.

Treatment of Feline Gastrointestinal Small-Cell Lymphoma With Chlorambucil and Glucocorticoids

Timothy J. Stein, DVM, PhD, Diplomate ACVIM (Oncology), MacKenzie Pellin, BS, Howard Steinberg, VMD, PhD, Diplomate ACVP, and Ruthanne Chun, DVM, Diplomate ACVIM (Oncology)

Treatment with chlorambucil and a glucocorticoid resulted in clinical remission in 27 (96%) of 28 cats, with a median duration of 786 days for the first clinical response [Figure 1].

All cats initially received chlorambucil at a dosage of 20 mg/m² orally once every 2 weeks. Because of client preference, two cats were switched to 20 mg/m² chlorambucil orally once every 3 weeks. Seventeen (60%) of the 28 cats received prednisone or prednisolone at 2 mg/

The median number of chlorambucil doses received per cat was 23 (range 5 to 110). Three treatment delays were reported as a result of hematological toxicities in cats treated with chlorambucil, one episode of a grade II thrombocytopenia, one episode of a grade II neutropenia, and one episode of a grade III neutropenia. None of the recorded toxicities required any additional therapy, and all resolved with treatment delay. Four (14%) of the 28

In the current study, chlorambucil was administered at 20 mg/m² every 2 weeks compared to 2 mg orally every 2 to 3 days. The administration of chlorambucil on a biweekly basis rather

HOW DO THEY DO?

- Toxicities
 - Chlorambucil
 - GI Signs (~20-25%)
 - Vomiting, diarrhea
 - Neutropenia
 - Typically rare, mild, resolves with tx delay
 - Hepatotoxicity
 - 10% of cats – resolves with stopping drug

Outcome and toxicity assessment of feline small cell lymphoma: 56 cases (2000–2010)

Kendra V. Pope*, Alex E. Tun*, Conor J. McNeill[†], Dorothy C. Brown* and Erika L. Krick*

*Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA and [†]Hope Advanced Veterinary Center, Vienna, Virginia, USA

ity was documented in 10.7% of patients. Overall response rate was 85.7% with glucocorticoid and chlorambucil. Median progression-free survival was 1078 days. Overall response rate for rescue chemotherapy was 59%. Reintroduction of prednisone and chlorambucil was associated with significantly longer survival than prednisone and lomustine (>1500 vs. 492 days, $P = 0.01$). Median overall survival times for cats with lymphoma of

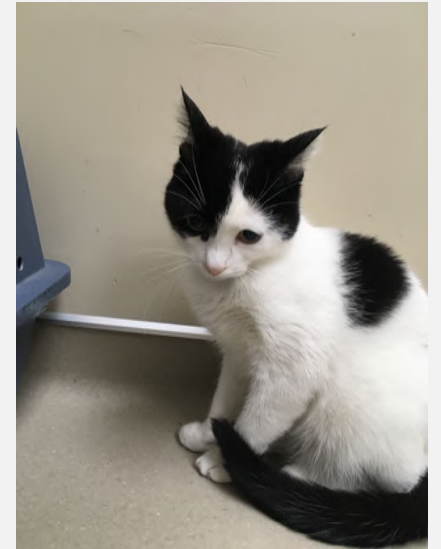
Initial response rate 86%

Median progression free survival = 1078 days!!

Dosing of chlorambucil was quite variable

ROXY

- How did we treat Roxy?
- Prednisolone 15mg PO once daily for 30 days
 - To be tapered after that once clinical signs are completely resolved
- Chlorambucil
 - 2mg PO once daily for 7 days, then every other day
 - Recheck CBC in 1 week
- Dietary management
 - Owners asked about Hypoallergenic diet, but also high fibre - they are looking into it

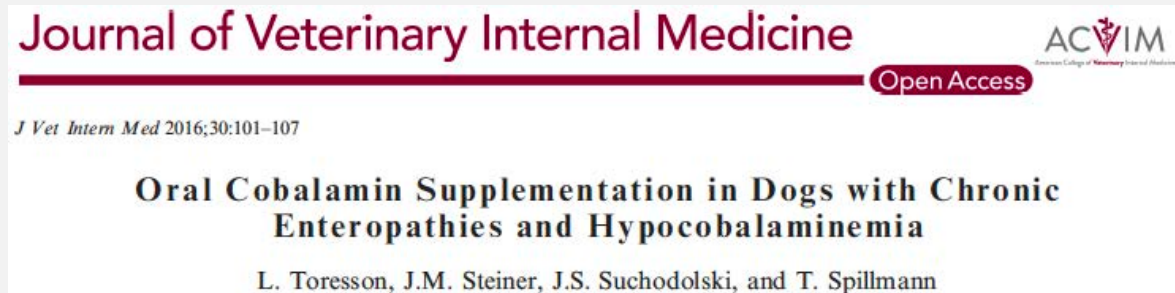


COBALAMIN (B12)

- Cobalamin deficiency is very common in chronic GI diseases!
 - Dogs and cats!
- Testing
 - Recommended in most of our chronic GI work ups
 - Part of Texas A&M “GI Panel” along with TLI
- Supplementation
 - 250 to 1000 ug per dog SC once weekly for 4-6 weeks, then monthly after that
 - Ideally based on serum levels, however, can get expensive

ORAL COBALAMIN?

- Long thought to be poorly absorbed in patients with GI disease
 - Due to lack of intrinsic factor and malabsorption
- People have been shown to absorb it orally
 - Seemingly through a different pathway than normal (i.e. without intrinsic factor)
- Two recent retrospective papers looks at oral cobalamin supplementation in dogs and cats
 - Both found that patients receiving oral cobalamin had increased serum levels after administration
 - Oral 1mg tablets



Short Communication



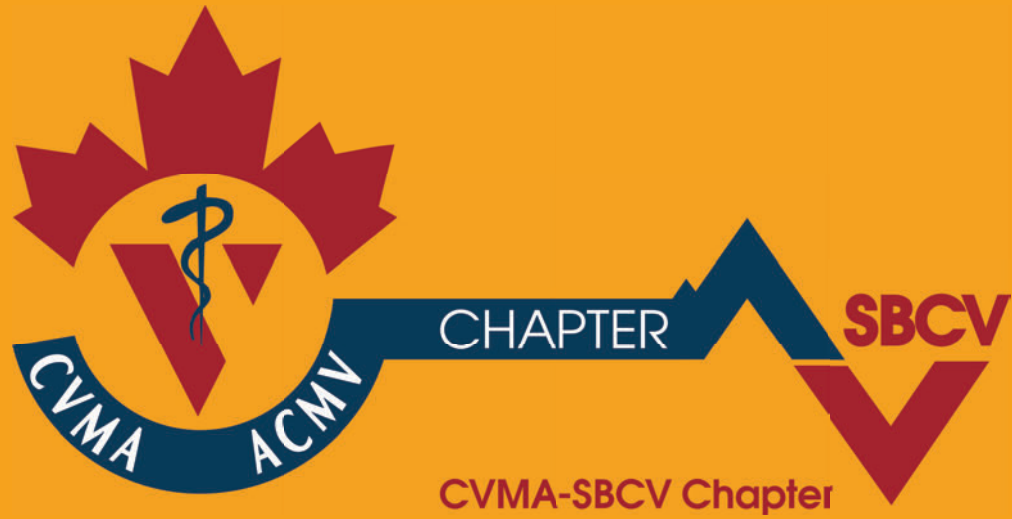
jfms
Journal of Feline
Medicine and Surgery

Oral cobalamin supplementation in cats with hypocobalaminemia: a retrospective study

Linda Toresson^{1,2}, Joerg M Steiner³, Gunilla Olmedal²,
MajBritt Larsen², Jan S Suchodolski³ and Thomas Spillmann¹

Journal of Feline Medicine and Surgery
2017, Vol. 19(12) 1302–1306
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SAGE



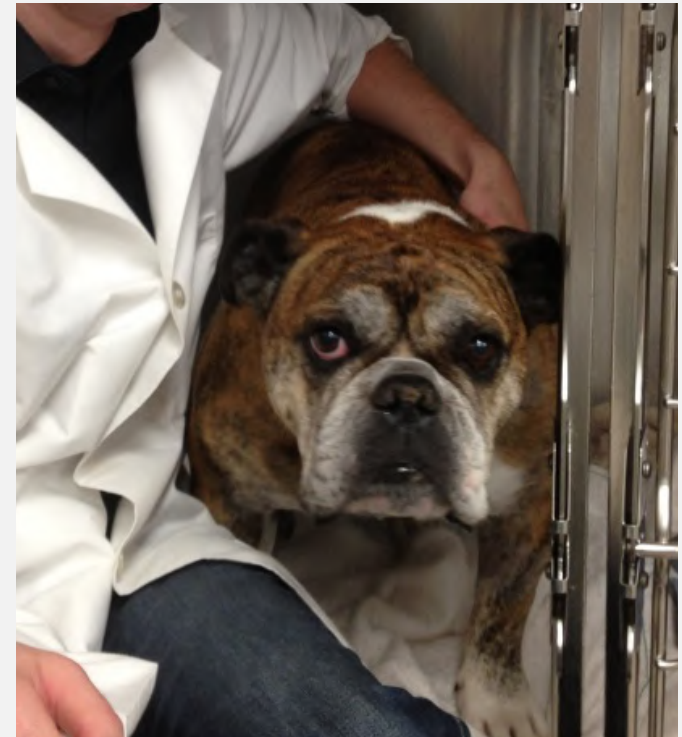
QUESTIONS?

Thank you all for listening and to the SBVC for inviting me to speak

LARGE INTESTINAL DISEASE

KALLIE

- 10 year old FS English Bulldog
- 7 month history of intermittent, cyclical large bowel diarrhea
 - Increased frequency, urgency. Mucous, tenesmus



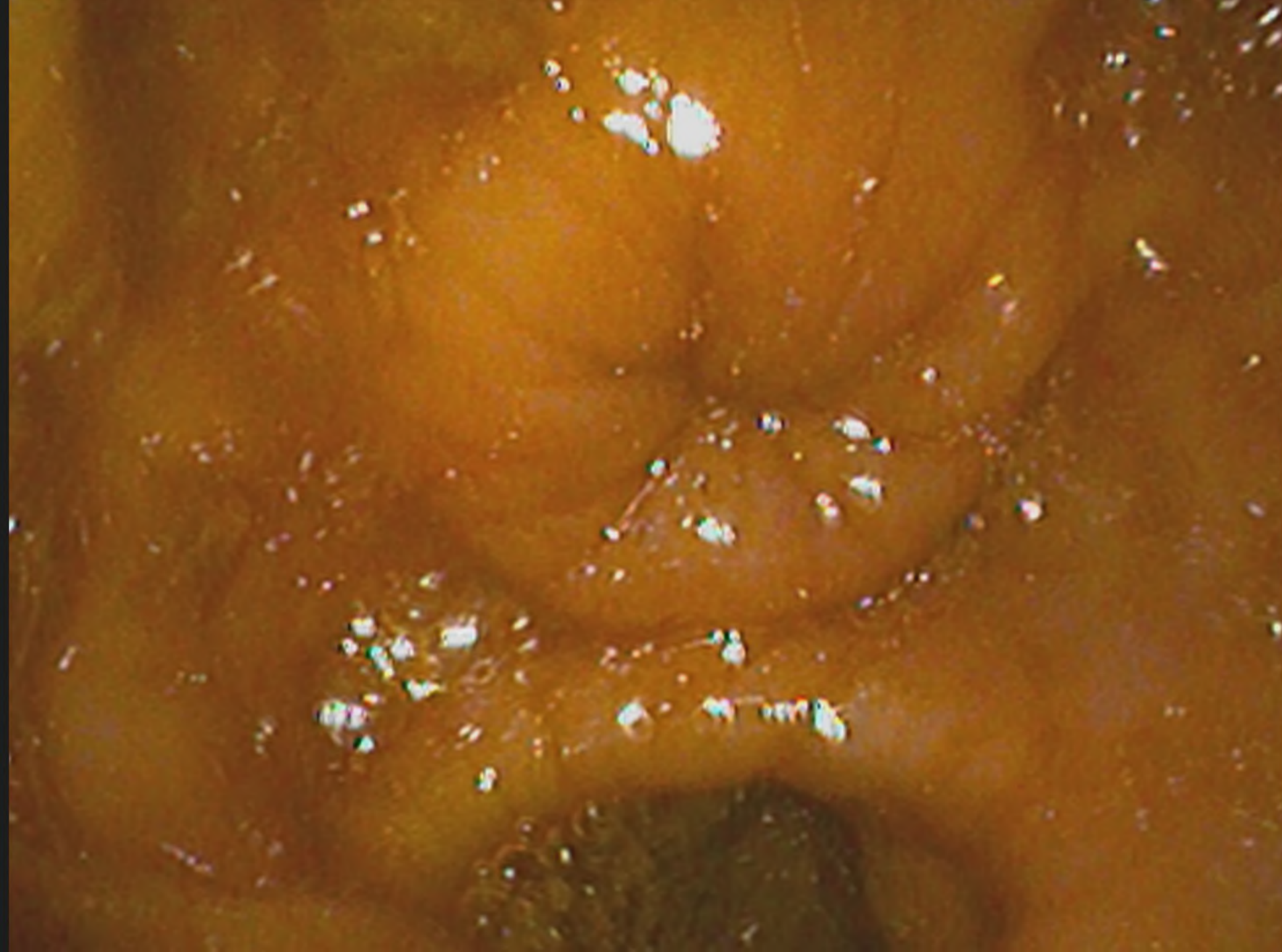
PREPARATION...

- How do we perform a colonoscopy and get adequate samples?
- Much debate over best way to prep a patient for colonoscopy
- Ideally:
 - 2 doses of PEG solution, given two hours apart via orogastric tube the evening before the procedure
 - 2 enemas the evening before the procedure
 - 1 enema the morning of the procedure
 - Fasted for 24 hours

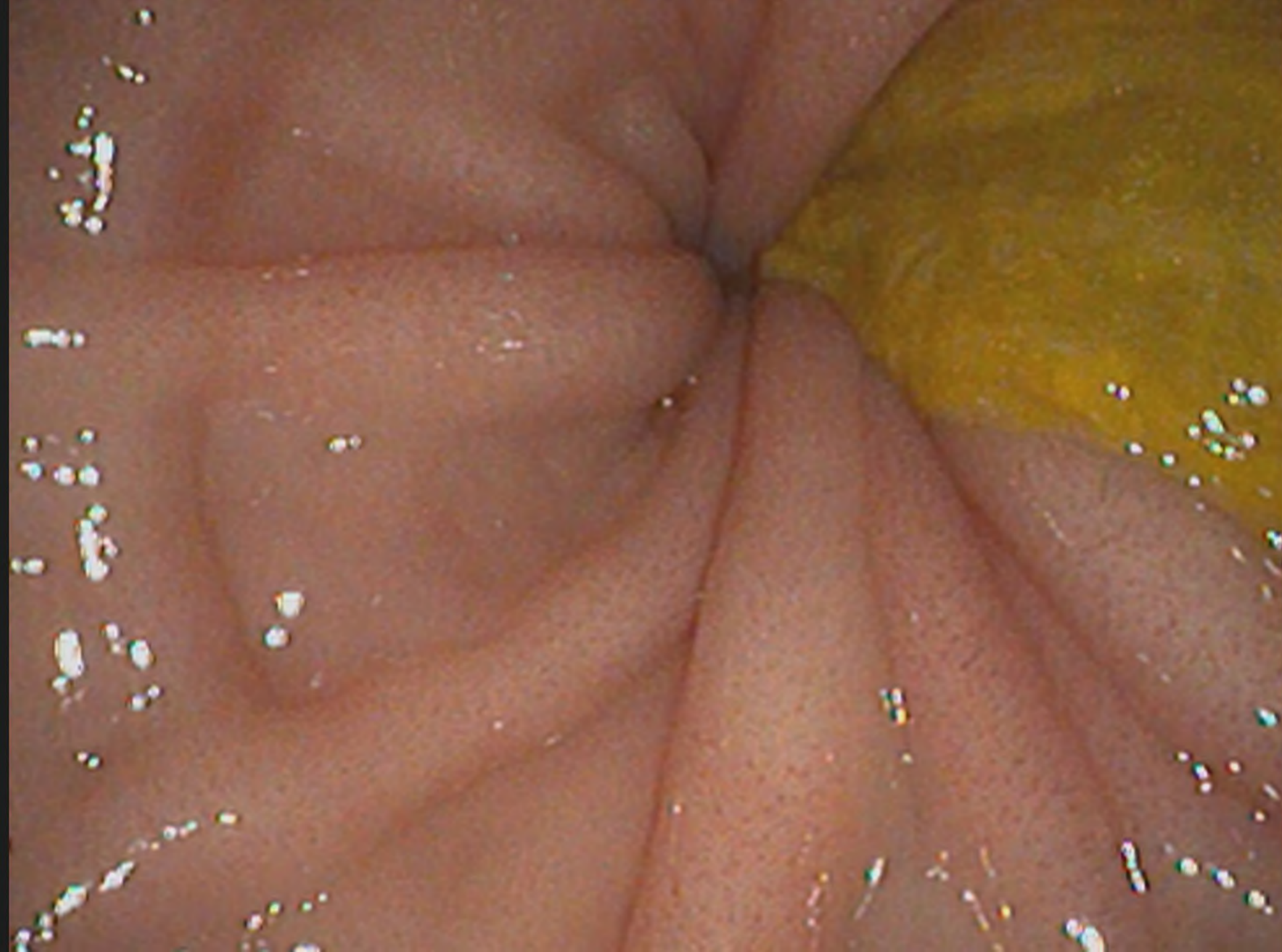
When was the last time something
when “ideally” for you?

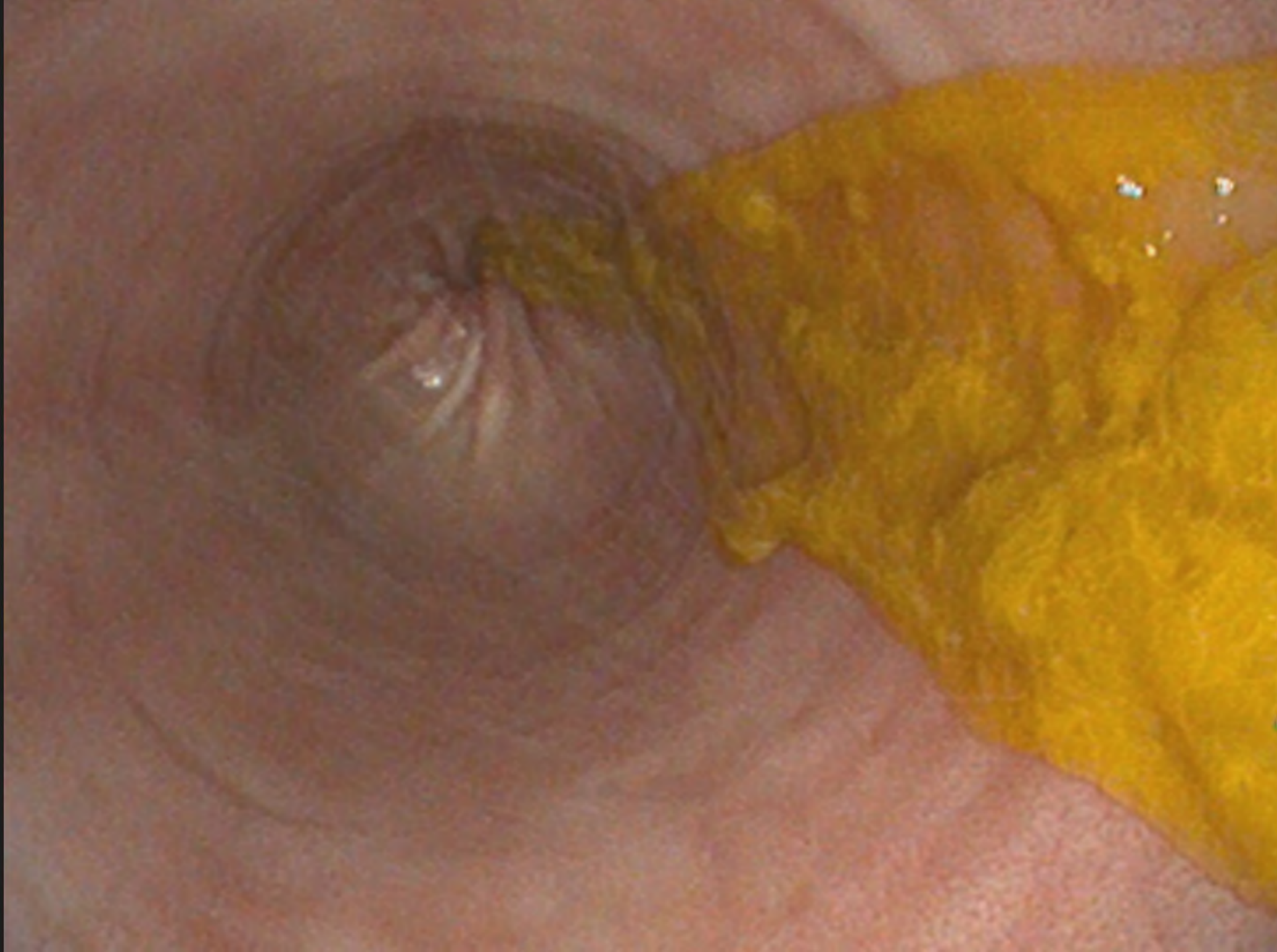
PREPARATION CONTINUED

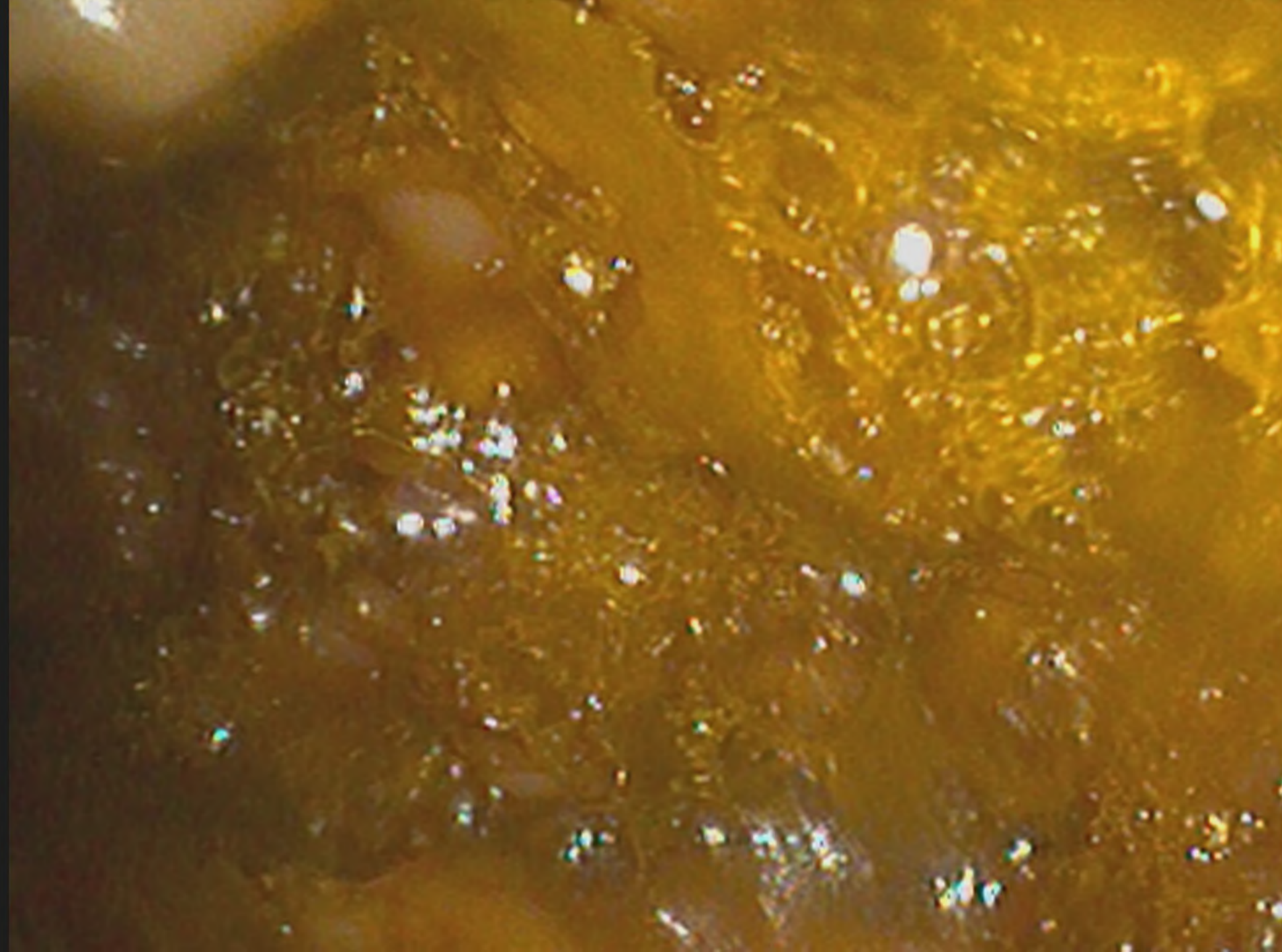
- Many many different “modified” routines
- For small dogs and cats:
 - Fasted for 24-48 hours
 - Enemas after under general anesthesia, prior to scoping
- For cats and dogs you don't want to pass an orogastric tube:
 - Place a NE or NG tube and administer a CRI of the PEG solution
 - Add on enemas evening before and the morning of the procedure
 - Fasting for 24-28 hours

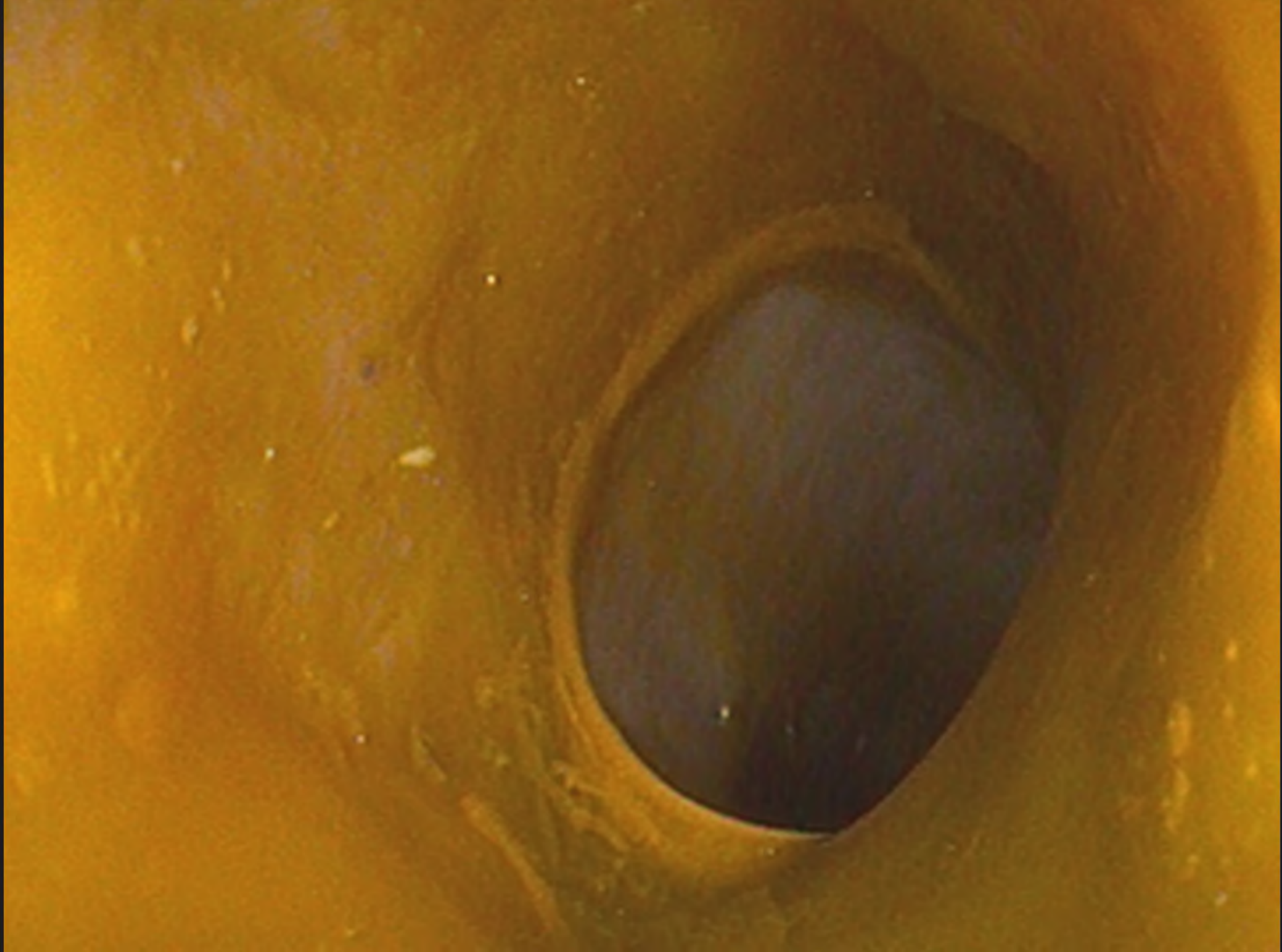












KALLIE

- Diagnosis:
 - Lymphoplasmacytic IBD
- But its only mild?!
 - Degree of histopathology inflammation doesn't have to correlate with clinical disease

Resident Pathologist: Timothy Wu, DVM, MS

Final Report

Morphologic Diagnosis:

Small intestine: within normal limits

Colon: Mild, diffuse, chronic, lymphoplasmacytic colitis

Comment:

In this case, the diagnostic quality of the samples is adequate, permitting confident histopathologic assessment. Based on the surface epithelial damage and mild lymphoplasmacytic infiltration, the histopathologic changes are most compatible with mild IBD. The inflammatory infiltrate is mild but the degree of inflammatory infiltrates has not been shown to be associated with clinical disease (Jergens et al. 2003. J Vet Intern Med. 17: 291-7).

COLITIS - DIFFERENTIALS

- Infectious
 - Parasites
 - Whipworms
 - Giardia
 - Bacterial
 - *Salmonella*
 - *Campylobacter*
 - Invasive *E. coli*
 - *Clostridium* spp.
 - Fungal
 - Histoplasmosis
 - Prototheca
 - Pythium
- Dietary
 - Indiscretion, intolerance, allergic
- Inflammatory
 - IBD
- Neoplastic
 - AC, LSA
 - Rectal polyps
- Structural
 - Strictures, intussusceptions, cecal eversions
- Functional
 - Secondary to small bowel disease
 - IBS (uncommon!)

COLITIS- TREATMENT

- Options are much like we have already discussed:
 - Diet, antibiotics, immunosuppressive
- There is no reliable way to predict which dogs will respond to what treatment or combination of therapies
- **MUST RULE OUT** that differential list before we arrive at a diagnosis of IBD!
 - Consider where your patient has been, deworming history, etc...
- A systematic approach beginning with diet, followed by antibiotics, then immunosuppressives is advocated by many
 - Though many owners are not super patients, so diet and antibiotics might go together!

DIETARY THERAPY

- Dietary options: Novel proteins vs. hydrolyzed proteins vs. easily digestible
 - Principles remain the same as with IBD mentioned before
 - Improvement within 1-2 if they are going to respond, but may take 4-12 weeks to see complete reponse
 - Several studies show dogs can relapse when switched back to a “normal diet”
 - So I tend to leave them on these diets for life
- Psyllium (Soluble Fibre)
 - This can be helpful in a subcategory of dogs with “Fibre-Responsive Large Bowel Diarrhea”
 - I recommend an OTC psyllium fibre powder, not pumpkin

COLITIS - TREATMENT

- Antibiotics
 - Metronidazole – which most of them have seen before they get to me!
 - Tylosin – as previously discussed, can be a good long term choice
- Immunosuppressives
 - Same concept as we discussed earlier. Same drug options, doses, tapering plans, etc...
- Alternative drugs
 - Sulfasalazine – anti-inflammatory bound to a carrier, dissociates in the large intestine
 - Direct topical anti-inflammatory action
 - Do need to monitor for KCS, as it can occur as with other sulfas

GRANULOMATOUS COLITIS

- Aka Histiocytic ulcerative colitis or Boxer colitis
- Definition:
 - Mucosal infiltration with macrophages with variable numbers of neutrophils, lymphocytes and plasma cells
 - The macrophages are PAS stain positive and usually are accompanied by mucosal ulceration and loss of goblet cells
 - FiSH identifies intramucosal *e.coli*
- Breeds
 - Boxers and French Bulldogs are the classic patients
 - Has been reported in Mastiff, Alaskan malamute, Doberman and English bulldogs

Granulomatous Colitis of Boxer Dogs

Melanie Craven, BVetMed, PhD, MRCVS^{a,*},
Caroline S. Mansfield, BVMS, MVM^b,
Kenneth W. Simpson, BVM&S, PhD^a



a in a young Boxer dog with severe GC.

J Vet Intern Med 2013;27:56-61

Association between Granulomatous Colitis in French Bulldogs and Invasive *Escherichia coli* and Response to Fluoroquinolone Antimicrobials

A.C. Manchester, S. Hill, B. Sabatino, R. Armentano, M. Carroll, B. Kessler, M. Miller, B. Dogan, S.P. McDonough, and K.W. Simpson

GRANULOMATOUS COLITIS

- Clinical signs
 - Severe large bowel diarrhea
 - Profound weight loss
 - Sometimes accompanied with anemia and hypoalbuminemia
- Diagnosis
 - Endoscopic biopsies
 - See the previous description of histo findings
 - FiSH
 - Identifies intracellular enteropathogenic e.coli that are the causative agent

WHAT DOES IT LOOK LIKE?

Granulomatous Colitis of Boxer Dogs

Melanie Craven, BVetMed, PhD, MRCVS^{a,*},
Caroline S. Mansfield, BVMS, MVM^b,
Kenneth W. Simpson, BVM&S, PhD^a

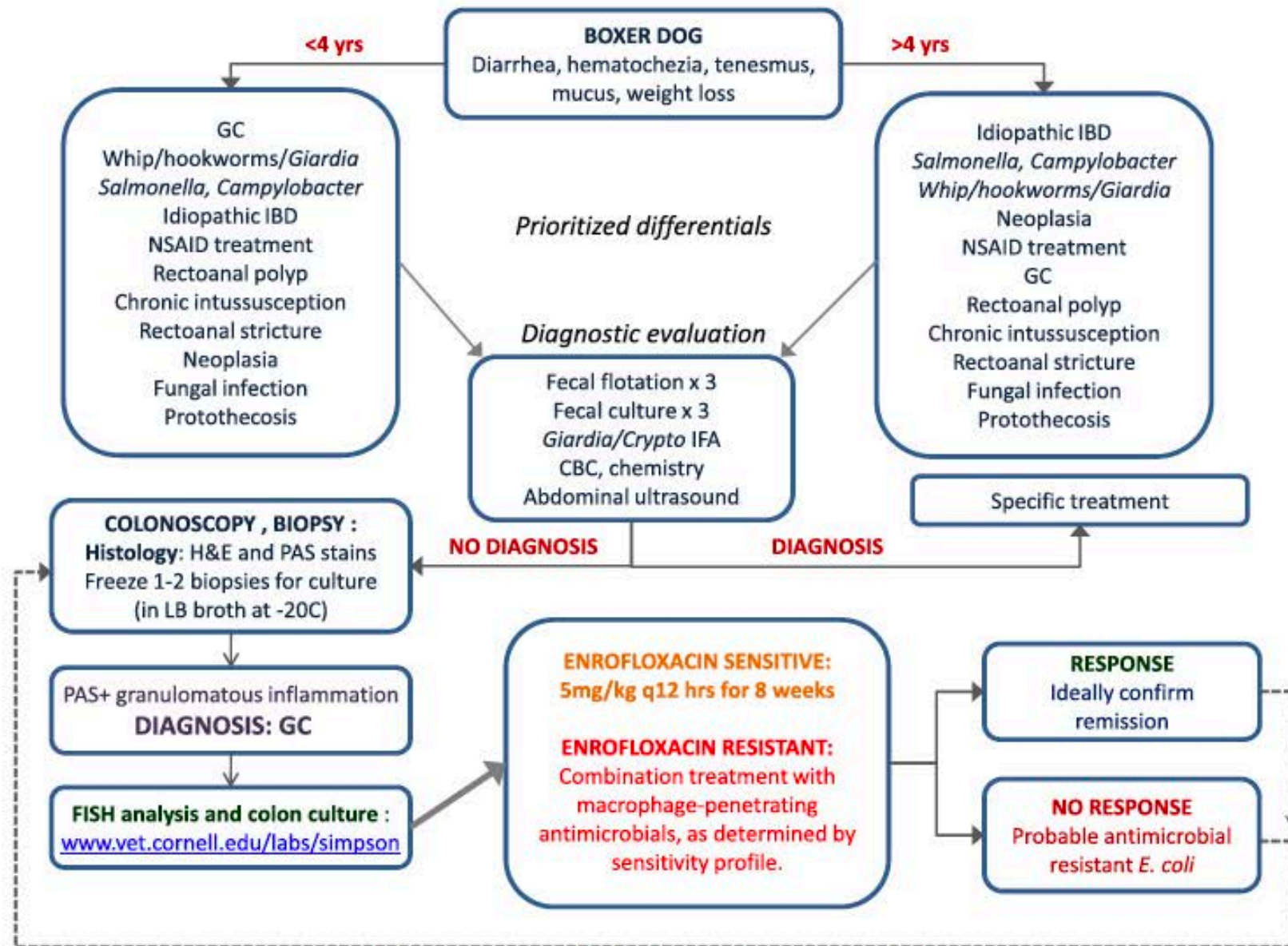
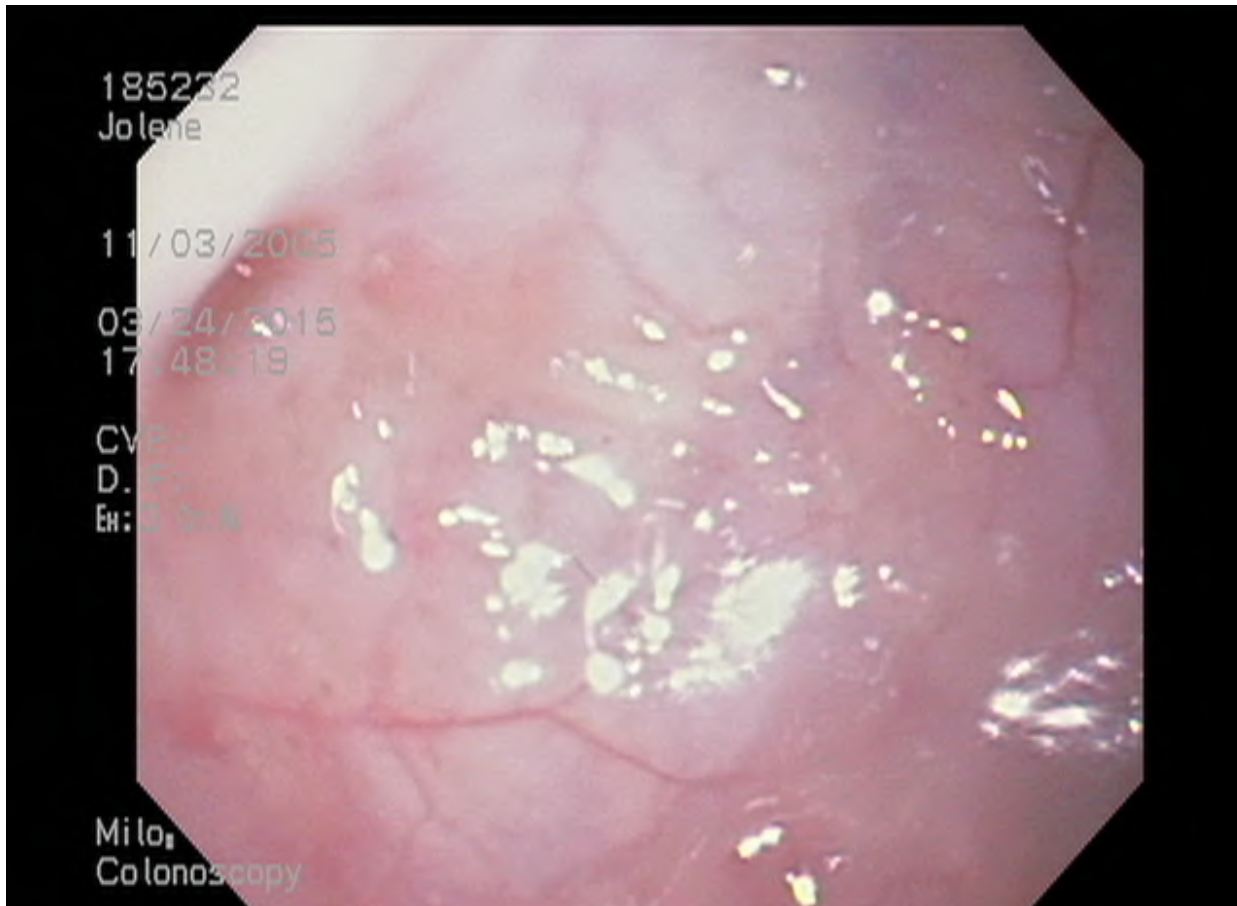


Fig. 5. Summary of the approach to diagnosis and treatment of GC. CBC, complete blood cell count; H&E, hematoxylin-eosin; IFA, immunofluorescence assay; NSAID, nonsteroidal antiinflammatory drug.

GRANULOMATOUS COLITIS

- Treatment:
 - Enrofloxacin 10 mg/kg PO SID x 8 weeks
 - This is a LONG duration of treatment
 - Shorter durations of therapy have resulted in reports of resistance, often to multiple classes of antimicrobials
 - Leaving few drugs available to treatment (i.e. chloramphenicol)
 - These patients do not respond to empirical or “standard” IBD/colitis therapies
 - Immunosuppression or diet changes aren’t enough



CAT COLON

Remember where LSA happens:

- Jejunum

We can't get there, but we can get to ileum via colonoscopy

185222

Jolene

11/03/2005

03/24/2015

17:49:26

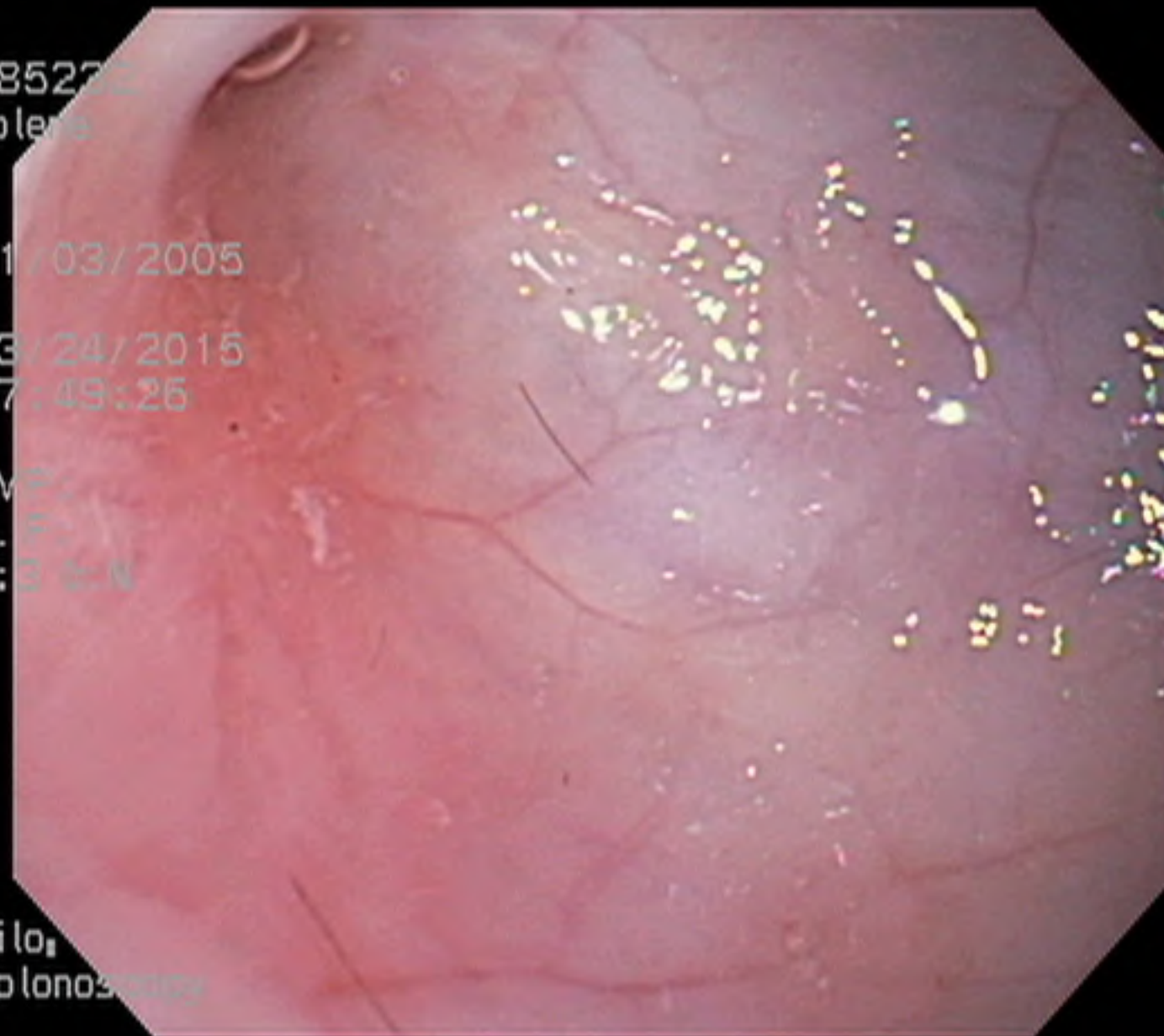
CVP

D. F.

En: 3 0: N

Milo,

Colonoscopy



185232

Jolene

11/03/2005

03/24/2015

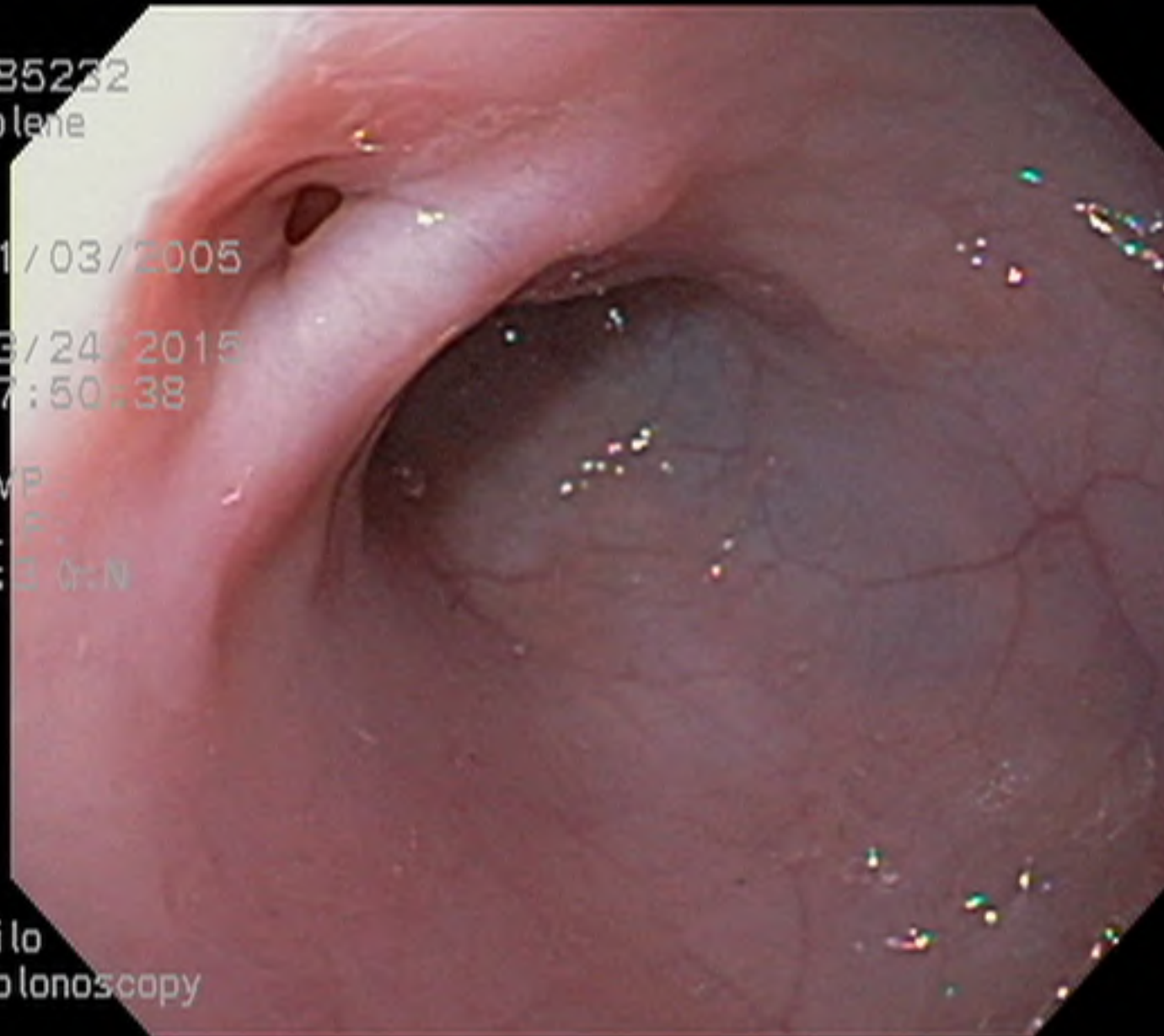
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CVP

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En: 3 0: N

Milo
Colonoscopy



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Jolene

11/03/2005

03/24/2015

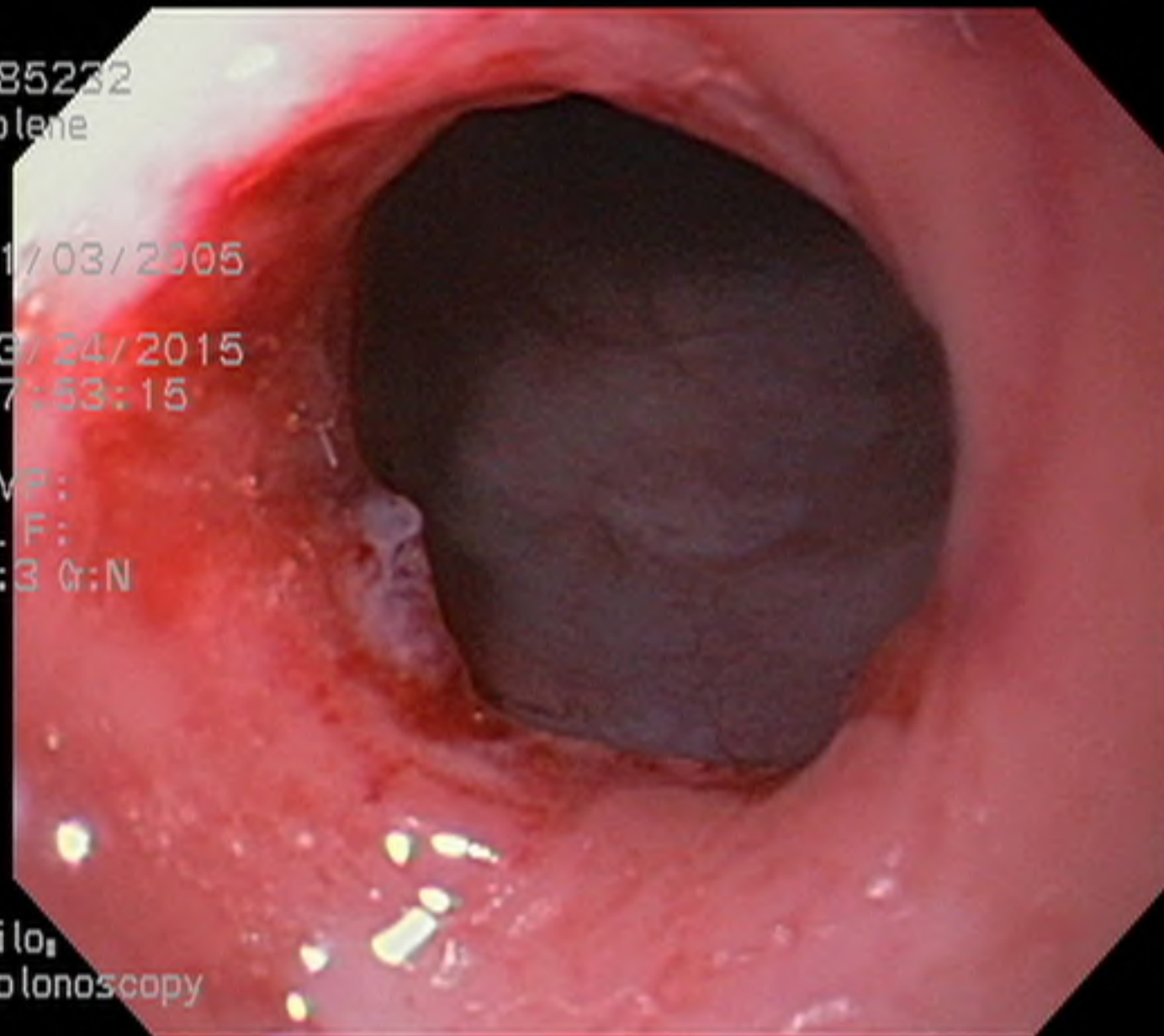
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CVP:

D. F:

Et: 3 Gr: N

Milo,
Colonoscopy



MISCELLANEOUS GI

An assortment of interesting variations on a theme

EXOCRINE PANCREATIC INSUFFICIENCY

- Signalment:
 - Typically 1-5 yrs old, but can be older too
 - Atrophic pancreatitis vs result of chronic pancreatitis/fibrosis
 - German shepherds, rough coated collies, Eurasians
- Clinical signs:
 - Increased fecal volume and frequency of defecation
 - Grey/yellow feces (“bird seed” appearance)
 - Polyphagia *and* weight loss
 - Flatulence
 - Abdominal discomfort from bloating/intestinal gas
 - Sometimes can have skin disorders concurrently

TESTING FOR EPI

- Serum Trypsin-like Immunoreactivity
 - Highly sensitive and specific for the diagnosis of EPI in dogs and cats
 - The measured trypsin and trypsinogen originates only from pancreas and reflects amount of functional tissue present
 - < 2.5 ug/L for dogs and < 8.0 ug/L for cats *along with clinical signs* is diagnostic
 - Retest “grey zone” results in 4 weeks (2.5 – 5.7 for dogs, 8.0 – 12 for cats)
 - A single sample is sufficient
 - Fasting for 8-12 hours prior to collection
 - Sources of error – non fasting samples, decreased GFR (i.e. renal disease) can cause mild increases which may mask true disease

FECAL ENZYME MEASUREMENTS

- Canine Fecal Elastase
 - Not useful for a diagnosis, but can be helpful to exclude EPI
 - Very rarely used, but you might read about it...
 - A single measurement of > 20 ug/g will rule out EPI
 - LOTS of false positives
 - Always use TLI to confirm

CANINE EPI TREATMENT

- Enzyme Replacement Therapy
 - The highest enzyme activity in the duodenum is achieved with non-enteric coated supplements (but coated ones can work too)
 - The exact dose depends on the formulation and dog, but they are quite safe
 - Give with a meal, 2x per day
 - Once appropriate body weight and control of clinical signs, can slowly taper dose to find a maintenance dose that works for each dog
- Antibiotics
 - Can be helpful initially to control clinical signs
 - Like “antibiotic responsive diarrhea”
 - Tylosin or Metronidazole are the best options

COBALAMIN

- Deficiency occurs as a result of decreased uptake by intestinal bacteria as well as decreased intrinsic factor
 - 82% of dogs with EPI are cobalamin deficient
- Testing is easy
 - All part of the same panel (with TLI)
- Supplementation is important!
 - Parenteral vs. Oral
 - I still start with parenteral, even with the information on oral I presented to you earlier


EPI DIETARY MANAGEMENT

- You don't HAVE to change the diet, most can stay on their normal food
- SOME will benefit from changes:
 - Highly digestible, low fibre, moderate fat diet can reduce frequency and volume of defecation
 - Fat digestion can be difficult and enzymes won't fix that, so fat restriction may be helpful
 - But reduces calories, so can make it hard to put weight on
- Some dogs can develop dietary sensitivities as a result, so hypoallergenic diets may have a role in some cases
 - Novel protein or hydrolyzed protein diets

EPI AND CATS

- Reported as rare – but I think this happens more often than we realize!
- How does it differ from dogs?
 - It's the result of chronic pancreatitis, not the acinar atrophy of GSDs
- Signalment:
 - Older cats (think who gets chronic pancreatitis)
- Diagnosis
 - TLI – same as dogs, just as great a test
 - Cobalamin – often *severely* decreased in these patients, so important to check!

EPI AND CATS

- Looks like a lot of other cat diseases!
- Polyphagia and weight loss  **Best Internal Medicine differential ever!**
 - EPI
 - Hyperthyroidism
 - DM
 - Early CKD
 - GI lymphoma
- Old cats often have more than one thing going on at a time!
 - So we have to remember to look!

CAT EPI TREATMENT

- Enzyme supplementation
 - Works just like it does in dogs
 - Usually ½ tsp per meal, two meals per day
 - Can use raw pancreas, but who really wants to??
- Diet
 - Usually don't require diet modification
- Cobalamine
 - 250 ug/cat SC weekly for 4-6 weeks, guided by serum measurements

CAT DIARRHEA: *TRITICHOMONAS FOETUS*

- Generally occurs in younger cats, often from catteries/shelters
 - Can occur in older cats as well
- Large bowel diarrhea (mucous, hematochezia, tenesmus)
 - Signs may be persistent or intermittent
- Typically otherwise healthy
- If left untreated, most cats have resolution of signs within 2 years, but can shed or relapse for >6+ years
 - Source of infection for other cats...asymptomatic carriers

TTF DIAGNOSIS

- NC State,
www.JodyGookin.com
- PCR
 - Far and away the best method
 - Diarrhea (not formed feces)
- Direct Smears
 - Less than 2% positive
 - Can be helpful in cattery/shelter situations

Polymerase Chain Reaction Testing for Feline *T. foetus* Infection

- Sample Submission Form -

ANIMAL NAME_____	CLINICIAN_____
BREED_____	CLINIC NAME_____
SEX_____AGE_____	ADDRESS_____
DATE SAMPLE COLLECTED_____	CITY_____STATE____ZIP_____
TEL_____	EMAIL_____

DIRECT SMEAR PERFORMED? YES NO
FLAGELLATED ORGANISMS SEEN? YES NO
HOUSING: SINGLE CAT MULTIPLE CATS
FECAL COLLECTION: VOIDED LOOPED FLUSHED

IF TREATED, WITH WHAT?

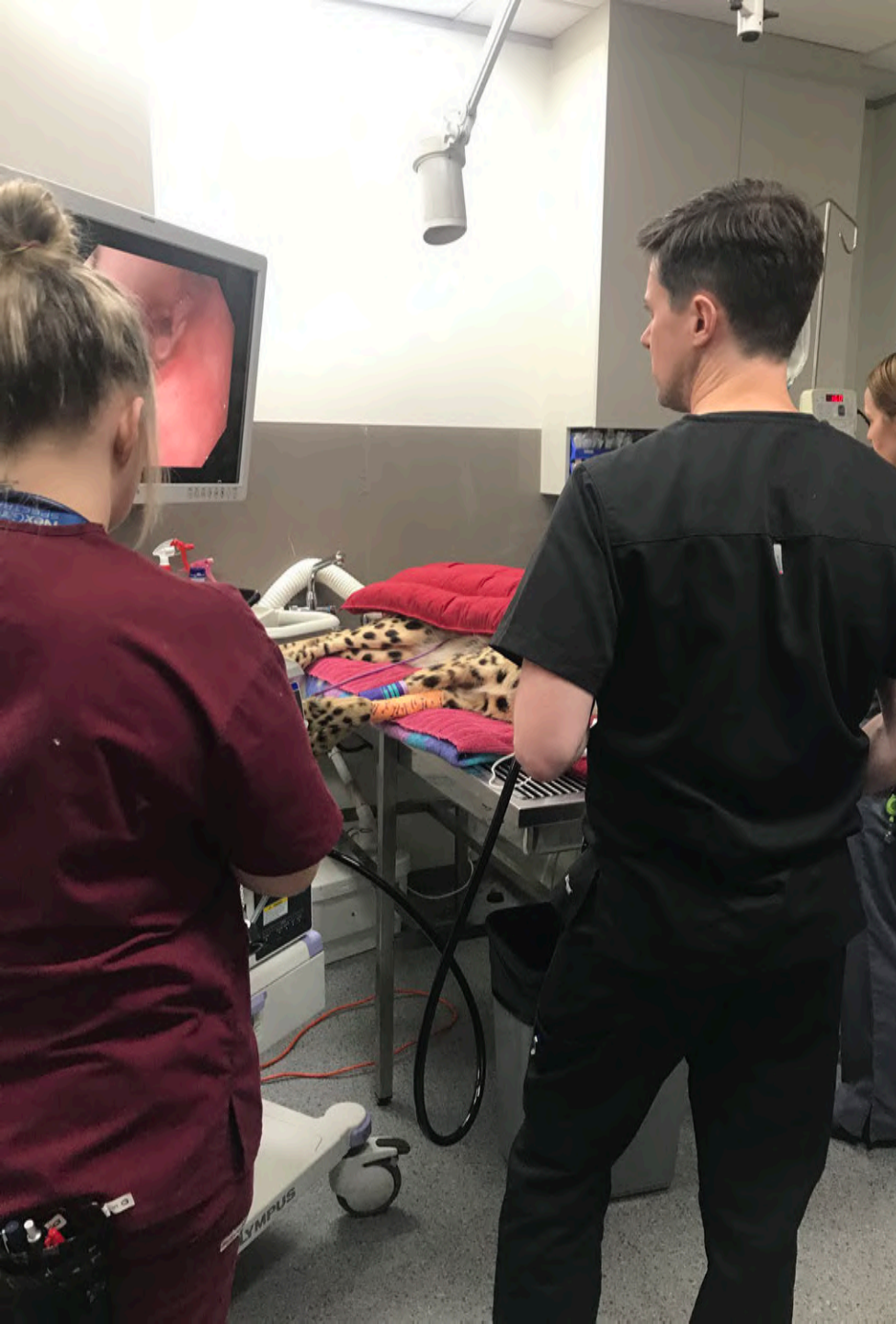
REASON FOR SAMPLE SUBMISSION (ie. history of diarrhea, cyclic symptoms) :

Sample Requirements Samples must be submitted by a licensed veterinarian. Submit a lima-bean sized amount of fresh feces placed in a red-top vacutainer tube which has then been filled with rubbing alcohol (isopropyl alcohol). Please place sample and submission form in separate ziplock bags. Refrigeration, freezing, or overnight shipment is not necessary. Feces must be diarrheic and free of litter. Formed samples rarely test positive even if occult infection is present. Samples collected with a loop or colon 'flush' are preferable. Allow 'flush' samples of feces to settle then discard the saline and add isopropyl alcohol to the sediment. Cats should not be receiving any antibiotics within several days prior to or at the time of testing.

Testing Cost

TTF TREATMENT

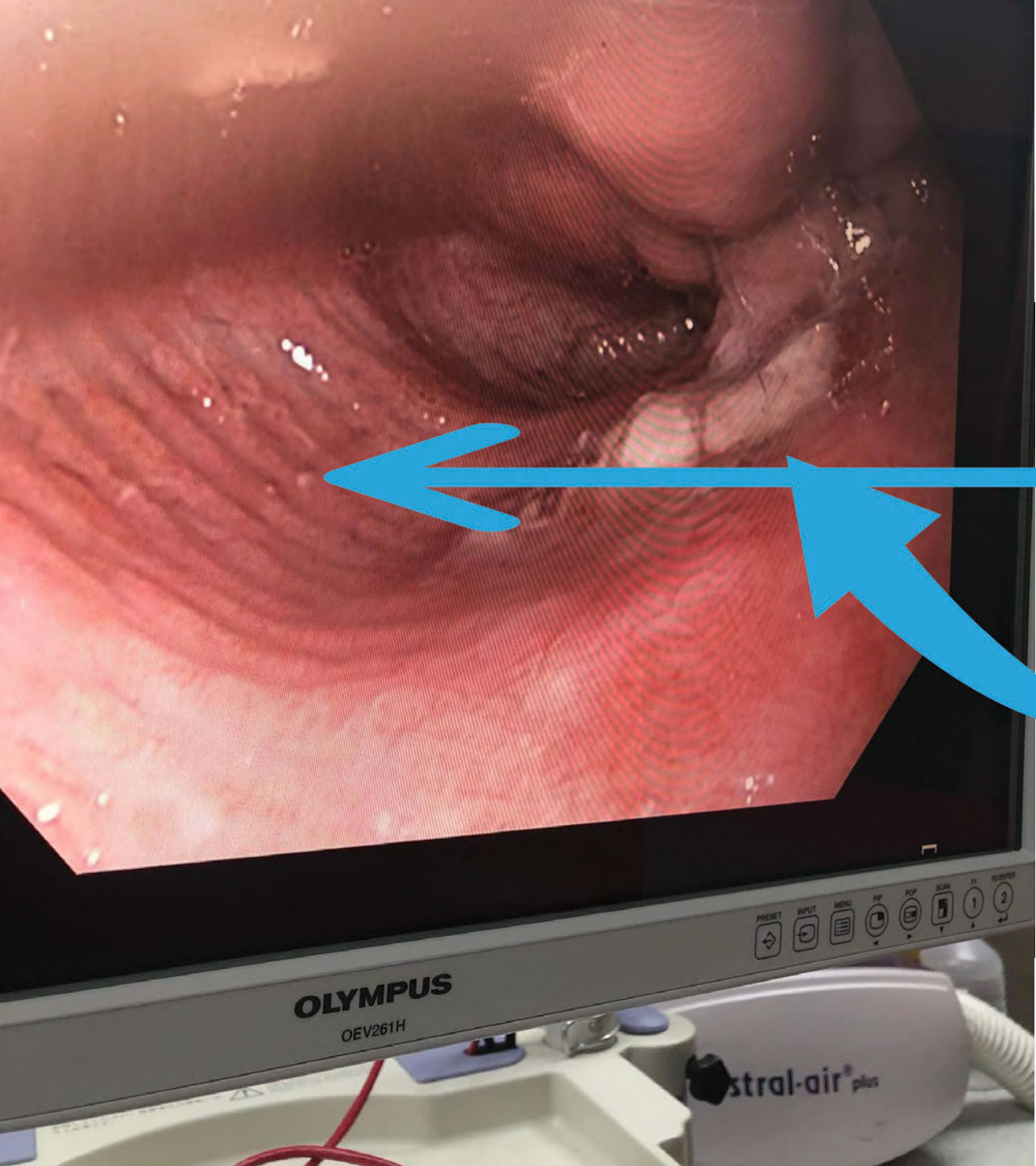
- Ronidazole
 - 5-nitroimidazole
 - Metabolized by the organism into cytotoxic nitro anions that disrupt TTF DNA
 - The *only* drug with convincing efficacy - metronidazole resistance widespread
 - Narrow margin of safety with this drug!
 - **30mg/kg PO ONCE daily for max of 14 days**
 - Dose dependent neurotoxicity
 - Mild – lethargy, anorexia
 - Severe – ataxia, seizures
 - It is vile tasting – needs to be compounded (recommend capsules and not liquids)



Name changed to protect the innocent

“SPOT”

- Signalment: 3-year-old intact male felid
- Presenting Complaint:
 - Intermittent anorexia, regurgitation, lethargy
 - Occasional vomiting
- Is an outdoor cat, so a bit hard to supervise, but lives in a controlled area so no access to toxins
- Diet has not changed:
 - Various meats, blood popsicles
- Current medications:
 - Omeprazole, sucralfate – both once per day – no change since starting

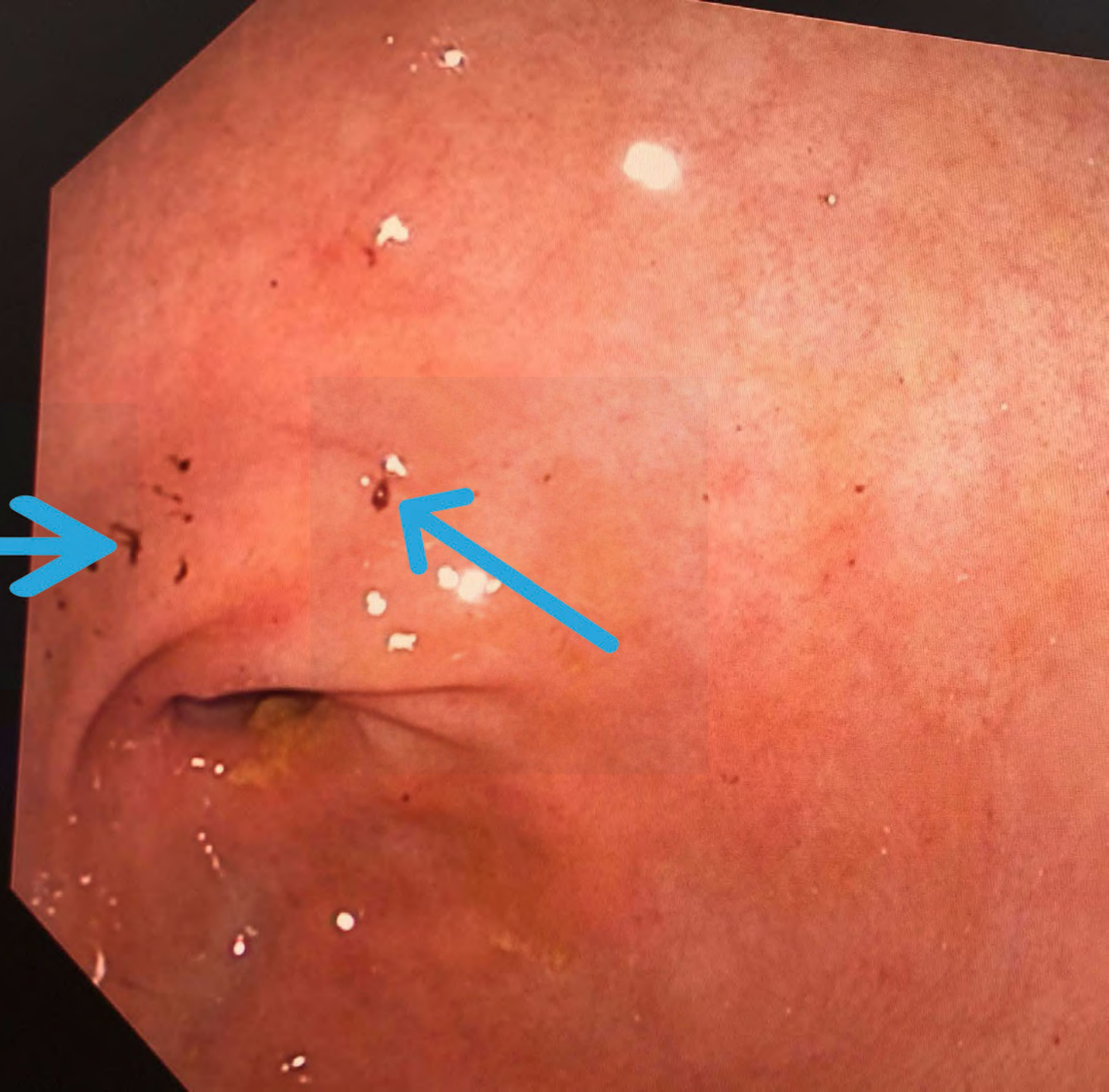


ENDOSCOPY

- “Ringed” appearance is normal for a feline
 - Even house cats
- Marked esophageal erythema
- Distal esophageal “mass” or proliferative tissue from an ulceration in the wall
- Collected biopsies from the proliferative tissue and the tissue adjacent to it

ENDOSCOPY CONTINUED

- Pyloric antrum moderately hyperemic and mottled
- Multiple small ulcers
- Interesting side note:
 - **GIGANTIC STOMACH!**
 - Has to hold a large carcass
 - Was quite difficult to distend and explore
 - Had to do it in sections



RESULTS AND TREATMENT

- Biopsies found marked eosinophilic inflammatory disease
- Treatment
 - Budesonide, once daily in a blood popsicle
 - We chose this because of ease of administration
 - Tablet size
 - The “owner” had it on hand
 - Response
- Within 2-3 days of starting therapy, the clinical signs resolved and “Spot” had markedly increased appetite and energy



Original Article

jfms
Journal of Feline
Medicine and Surgery

Clinicopathological and ultrasonographic features of cats with eosinophilic enteritis

Journal of Feline Medicine and Surgery
2014, Vol. 16(12) 950–956
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DOI: 10.1177/1098612X14525385
jfms.com



Samuel Tucker¹, Dominique G Penninck¹, John H Keating²
and Cynthia RL Webster¹

Abstract

Eosinophilic enteritis (EE) in cats is poorly characterized. The aim of the current study was to retrospectively evaluate the clinical and ultrasonographic findings in cats with histologic evidence of eosinophilic inflammation on gastrointestinal biopsy. Twenty-five cats with tissue eosinophilia on surgical (10) or endoscopic (15) biopsy of the gastrointestinal tract, having an abdominal ultrasound performed within 48 h of biopsy acquisition, were enrolled. History, clinical presentation, clinical pathology and abdominal ultrasound findings were reviewed. Intestinal biopsies were evaluated by a single pathologist and separated into two groups based on the degree of eosinophilic infiltrate: mild (<10 eosinophils/high-power field [HPF], 11/25 cats), or moderate/marked (>10 eosinophils/HPF, 14/25 cats). The former were considered primary lymphoplasmacytic or lymphocytic inflammatory bowel disease (LPE) with subtle eosinophilic infiltrates, and the latter to have EE. Signalment, history and clinical signs were similar in all cats. Only cats with EE (6/14) had palpably thickened intestines. The only distinguishing clinicopathological feature of cats with EE was the presence of peripheral eosinophilia (6/14). On ultrasound, when compared with cats with LPE, cats with EE had a greater mean jejunal wall thickness (3.34 mm ± 0.72 mm vs 4.07 mm ± 0.58 mm, respectively) and an increased incidence of thickening of the muscularis layer (1/11 and 11/14, respectively). In conclusion, ultrasonographic evidence of a prominent intestinal muscularis layer, palpably thickened intestines and peripheral eosinophilia can serve as biomarkers for the presence of EE in cats with chronic intestinal signs.

TYSON

- 8 year old MN Boston Terrier
- Chronic vomiting (since July 2019)
 - Sometimes softer stool, maybe darker in color
- Owners were unclear on what had been done
 - Bland diet
 - Antiemetic
 - No further work up
- Vomiting persisted
- Recently developed a cough, which is what brought them to their new vet in April



CBC JULY 2019

- Mild regenerative anemia
 - Microcytic, hypochromic
- Thrombocytosis
 - May become important later...
- Non-inflammatory

TEST	RESULT	REFERENCE VALUE	
RBC	6.30	5.50 - 8.50 x10 ¹² /L	
Hematocrit	0.323	0.37 - 0.55 L/L	L
Hemoglobin	94	120 - 180 g/L	L
MCV	51.3	60.0 - 77.0 fL	L
MCH	14.9	18.5 - 30.0 pg	L
MCHC	291	300 - 375 g/L	L
RDW	18.9	14.7 - 17.9 %	H
% Reticulocyte	2.3	%	
Reticulocytes	147.9	10.0 - 110.0 K/μL	H
WBC	5.95	5.50 - 16.90 x10 ⁹ /L	
% Neutrophils	76.1	%	
% Lymphocytes	12.3	%	
% Monocytes	9.4	%	
% Eosinophils	1.8	%	
% Basophils	0.4	%	
Neutrophils	4.53	2.00 - 12.00 x10 ⁹ /L	
Lymphocytes	0.73	0.50 - 4.90 x10 ⁹ /L	
Monocytes	0.56	0.30 - 2.00 x10 ⁹ /L	
Eosinophils	0.11	0.10 - 1.49 x10 ⁹ /L	
Basophils	0.02	0.00 - 0.10 x10 ⁹ /L	
Platelets	892	175 - 500 x10⁹/L	H
PDW	19.0	%	
MPV	8.2	fL	
Plateletcrit	0.73	%	

BIOCHEMISTRY JULY, 2019

- Chemistry – normal
 - ALB low normal 25 (23-40)
 - Glob low normal 29 (25-45)
 - Cholesterol normal 3.46 (2.84-8.26)



Consider the circumstances...

TEST	RESULT	REFERENCE VALUE	
Glucose	6.77	4.11 - 7.95 mmol/L	
IDEXX SDMA ^a	10	0 - 14 µg/dL	
Creatinine	57	44 - 159 µmol/L	
Urea (BUN)	6.0	2.5 - 9.6 mmol/L	
BUN: Creatinine Ratio	26		
Phosphorus	1.29	0.81 - 2.20 mmol/L	
Calcium	2.11	1.98 - 3.00 mmol/L	
Sodium	148	144 - 160 mmol/L	
Potassium	4.3	3.5 - 5.8 mmol/L	
Na: K Ratio	34		
Chloride	117	109 - 122 mmol/L	
Total Protein	54	52 - 82 g/L	
Albumin	25	23 - 40 g/L	
Globulin	29	25 - 45 g/L	
Albumin: Globulin Ratio	0.9		
ALT	73	10 - 125 U/L	
ALP	37	23 - 212 U/L	
GGT	4	0 - 11 U/L	
Bilirubin - Total	2	0 - 15 µmol/L	
Cholesterol	3.46	2.84 - 8.26 mmol/L	
Amylase	1,163	500 - 1,500 U/L	
Lipase	834	200 - 1,800 U/L	
Osmolality	296	mmol/kg	

TYSON

- April 30, 2020 CBC
 - Moderate, regenerative anemia
 - Microcytic, hypochromic
 - Thrombocytosis
 - Non-inflammatory
 - No spherocytes
- Coomb's negative
- Serum Iron: 7 (9-35)

HEMATOLOGY

TEST	RESULT	REF. RANGE/UNITS
L RBC	5.3	5.4 - 8.7 x10E12/L
L Hematocrit	0.25	0.38 - 0.57 L/L
L Hemoglobin	79	134 - 207 g/L
L MCV	47.2	59.0 - 76.0 fL
L MCH	14.9	21.9 - 26.1 pg
L MCHC	316.0	326.0 - 392.0 g/L
H RDW	23.5	10.0 - 19.0
% Reticulocyte	4.3	%
H Reticulocytes	227.9	10.0 - 110.0 x10E3/uL
L Reticulocyte Hemoglobin	12.6	22.3 - 29.6 pg
WBC	7.4	4.9 - 17.6 x10E9/L
% Neutrophils	79.9	%
% Lymphocytes	12.1	%
% Monocytes	4.5	%
% Eosinophils	3.5	%
% Basophils	0.0	%
Neutrophils	5.9	2.9 - 12.7 x10E9/L
L Lymphocytes	0.9	1.1 - 5.0 x10E9/L
Monocytes	0.3	0.0 - 1.2 x10E9/L
Eosinophils	0.3	0.0 - 1.5 x10E9/L
Basophils	0.0	0.0 - 0.1 x10E9/L
H Platelets	956	143 - 448 x10E9/L
Platelet Comments	Platelet assessment Increased No clumped platelets noted. Platelet morphology normal.	
RBC Morphology	Polychromasia (>6 /100X) Hypochromasia - Moderate Schistocytes - Mild (1-2 /100X)	
WBC Morphology	WBC Morphology Normal	

Icterus Index Normal
Lipemia Index ++

IMMUNOLOGY

TEST	RESULT	REF. RANGE/UNITS
Coombs' (37° C) ^a	Negative	



Regeneration is a really helpful indicator!

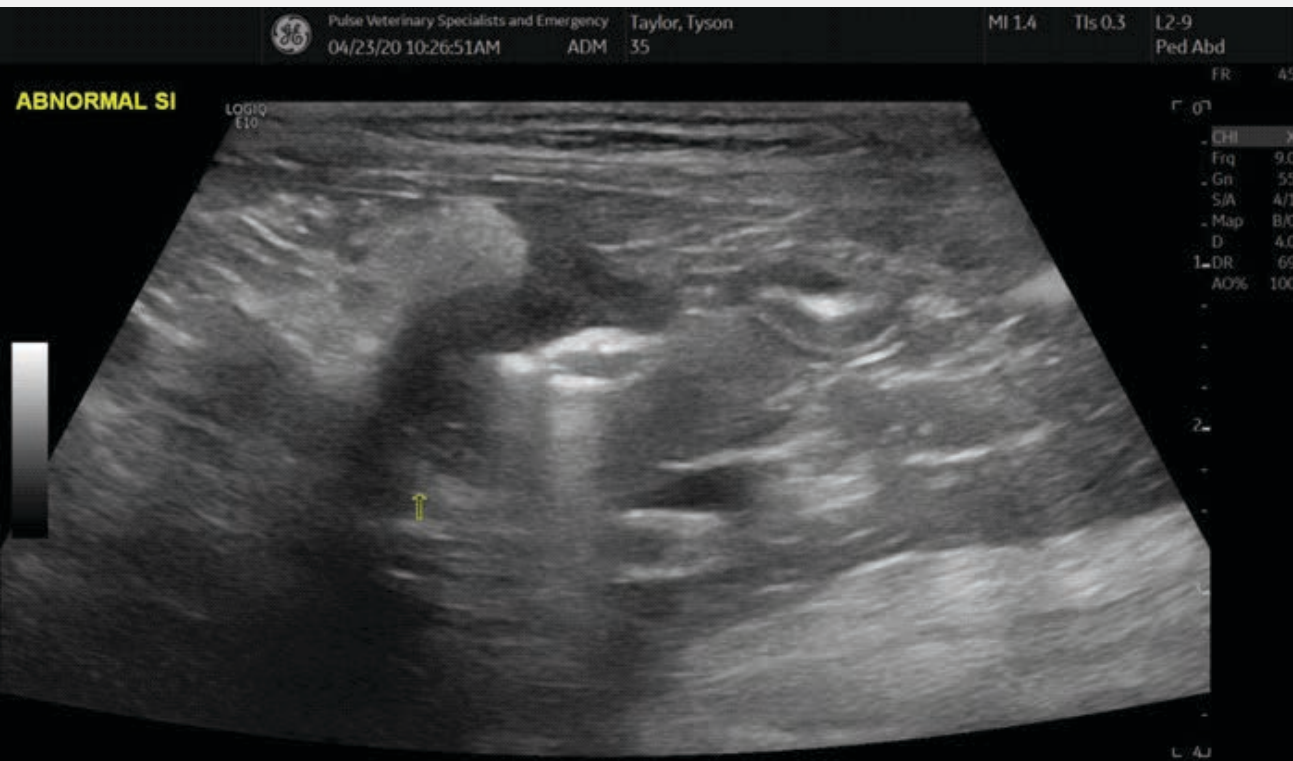
GI Bleeding is regenerative because the body can resorb all the raw materials

Can be the earliest sign of GI bleeding, even without an anemia!

ABDOMINAL ULTRASOUND

A focal section of distal duodenum with moderate circumferential wall thickening (up to 5.6mm thick) with loss of wall layering

FNA
nondiagnostic



MAY, 2020

- Referred to me for endoscopy
- Marked regenerative anemia
 - Severe microcytosis, hypochromic
 - Thrombocytosis
 - Mild neutrophilia, but normal WBC
- Electrolytes were normal

TEST	RESULT	REFERENCE VALUE	
RBC	4.59	5.65 - 8.87 x10¹²/L	L
Hematocrit	0.172	0.373 - 0.617 L/L	L
Hemoglobin	51	131 - 205 g/L	L
MCV	37.5	61.6 - 73.5 fL	L
MCH	11.1	21.2 - 25.9 pg	L
MCHC	297	320 - 379 g/L	L
RDW	29.2	13.6 - 21.7 %	H
% Reticulocyte	7.0	%	
Reticulocytes	323.1	10.0 - 110.0 K/μL	H
Reticulocyte Hemoglobin	12.6	22.3 - 29.6 pg	L
WBC	16.28	5.05 - 16.76 x10 ⁹ /L	
% Neutrophils	87.8	%	
% Lymphocytes	7.6	%	
% Monocytes	3.3	%	
% Eosinophils	1.1	%	
% Basophils	0.2	%	
Neutrophils	14.31	2.95 - 11.64 x10⁹/L	H
Lymphocytes	1.23	1.05 - 5.10 x10 ⁹ /L	
Monocytes	0.53	0.16 - 1.12 x10 ⁹ /L	
Eosinophils	0.18	0.06 - 1.23 x10 ⁹ /L	
Basophils	0.03	0.00 - 0.10 x10 ⁹ /L	
Platelets	1,170	148 - 484 x10⁹/L	H
PDW	11.9	9.1 - 19.4 fL	
MPV	11.8	8.7 - 13.2 fL	
Plateletcrit	1.38	0.14 - 0.46 %	H

WHAT DID WE DO?

- I recommended abdominal explore
 - Allows for a guaranteed biopsy and possible complete excision
- Why not endoscopy?
 - I can reach it, but will only get a good biopsy if it extends to the mucosal layer
 - Overlying inflammation can hide the mass
 - I can't take it out!!
- Surgery
 - Mass was right at the duodenal flexure, wrapped in the blood supply to the intestine
 - Was excised but with poor margins



GASTROINTESTINAL STROMAL TUMOURS

- Uncommon tumours in dogs
- Arise from mesenchymal cells
 - Hard to differentiate from other sarcomas, but IHC is allowing us to be better at it
 - Looking back, often reclassify leiomyomas/leiomyosarcomas as GISTs
- Can Palladia help?
 - Seems like it might, especially in dogs without complete excision or with metastatic disease
 - Slows progression
 - People receive similar drugs for a minimum of 3 years following resection

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STANDARD ARTICLE

Retrospective evaluation of toceranib phosphate (Palladia®) use in the treatment of gastrointestinal stromal tumors of dogs

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Background: Gastrointestinal stromal tumors (GISTs) are uncommon intestinal neoplasms in the dog. Literature regarding adjunctive therapy for GISTs in dogs is sparse. High-risk GISTs in humans respond to tyrosine kinase inhibition in the adjuvant setting.

Objectives: To review cases of toceranib phosphate use in dogs with GISTs and provide initial assessment of possible biological activity. A secondary aim was to evaluate patient and tumor characteristics for possible prognostic value.

Animals: Twenty-seven dogs with confirmed GISTs based on histopathology and immunohistochemistry treated with toceranib.

Methods: Retrospective study in which cases of toceranib use in dogs with GIST were solicited using the American College of Veterinary Internal Medicine Oncology and Small Animal Internal Medicine listservs.

Results: Five of 7 dogs with gross disease experienced clinical benefit (71%; 3 complete responses, 1 partial response, 1 stable disease). These included 2 dogs with durable responses after toceranib discontinuation. Median progression-free interval (PFI) in dogs with gross disease was 110 weeks (range, 36-155 weeks). Median PFI in dogs with microscopic disease was 67 weeks (range, 9-257 weeks). Metastasis at diagnosis ($P = 0.04$) and high mitotic index ($P < 0.001$) were associated with shorter PFI in toceranib-treated dogs.

Conclusions and Clinical Importance: Biological activity of toceranib is evident in dogs with gross disease. Metastasis of GIST at diagnosis, as well as high tumor mitotic index, was associated with shorter PFI in toceranib-treated dogs. Larger studies are needed to define postsurgical risk and refine the use of toceranib in dogs with gross and microscopic GIST.

KEYWORDS

DOG1, immunohistochemistry, KIT, mutation, progression-free interval, tyrosine kinase inhibitor

Abbreviations: AE, adverse event; CB, clinical benefit; CR, complete response; DOG1, discovered-on-GIST 1; FFPE, formalin-fixed paraffin-embedded; GIST, gastrointestinal stromal tumor; ICC, interstitial cell of Cajal; IHC, immunohistochemistry; NED, no evidence of disease; NSAID, nonsteroidal anti-inflammatory drug; PD, progressive disease; PDGFR, platelet-derived growth factor receptor; PFI, progression-free interval; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RTK, receptor tyrosine kinase; SD, stable disease; TKI, tyrosine kinase inhibitor; VCOG-CTCAE, Veterinary Comparative Oncology Group Common Terminology Criteria for Adverse Events; VEGFR, vascular endothelial growth factor receptor

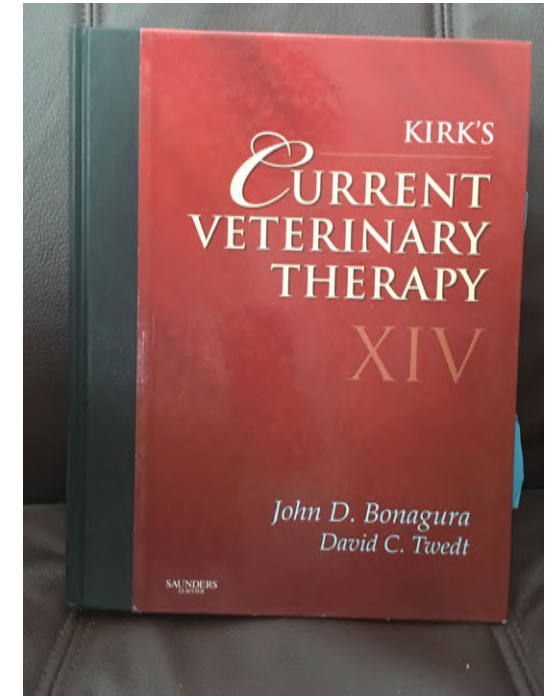
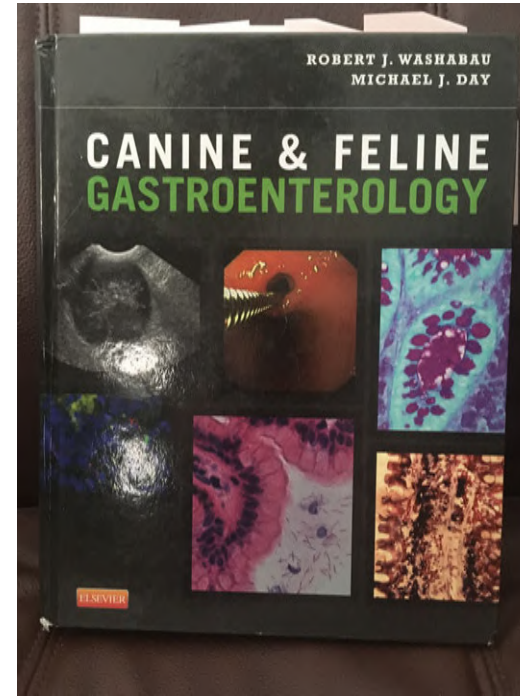
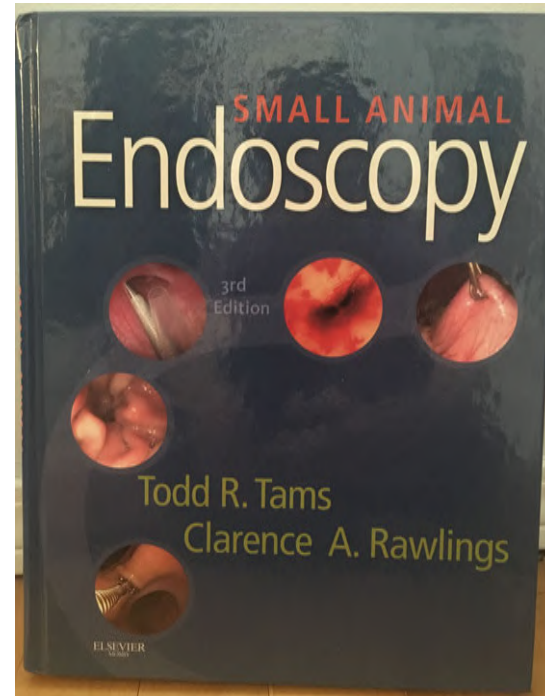
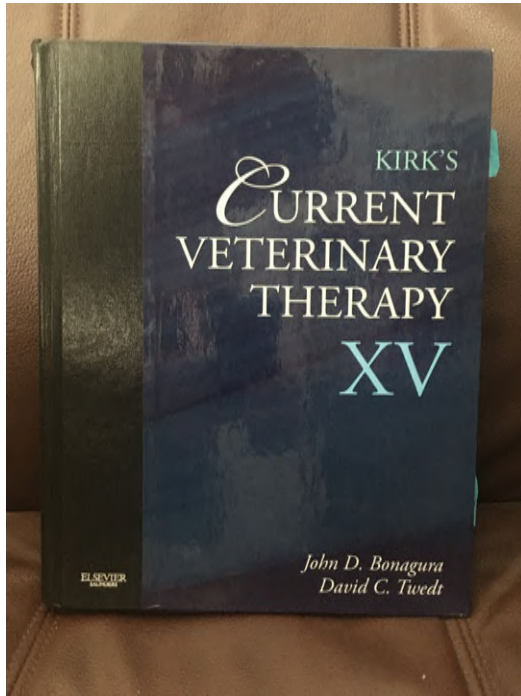
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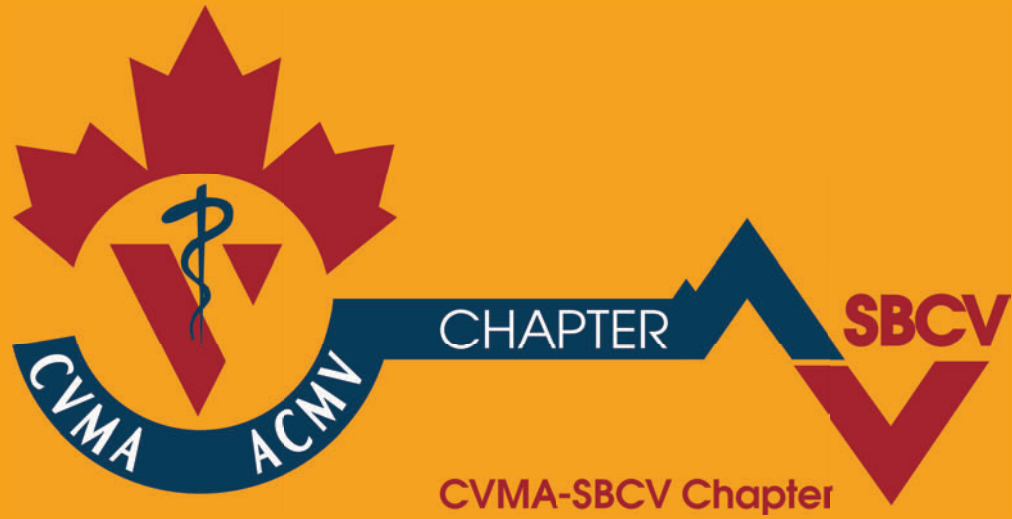
1 | INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal neoplasms arising from interstitial cells of Cajal (ICCs). They are rare in humans, but their true incidence in dogs is unknown.^{1,2} Differentiating GISTs from other gastrointestinal sarcomas is challenging because of their identical appearance under light microscopy. However, routine use of immunohistochemistry (IHC) has improved the ability to

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GOOD REFERENCES TO HAVE



QUESTIONS?

Thank you all for listening and to the SBVC for inviting me to speak