IMMUNOSUPPRESSIVE THERAPY

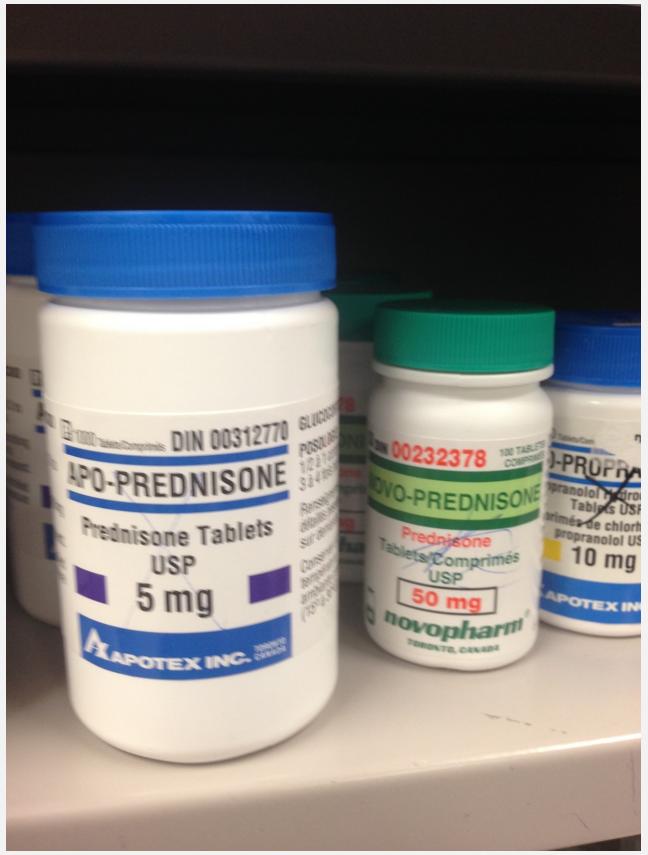
Which drugs are useful and how do we use them?

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
  - Want 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

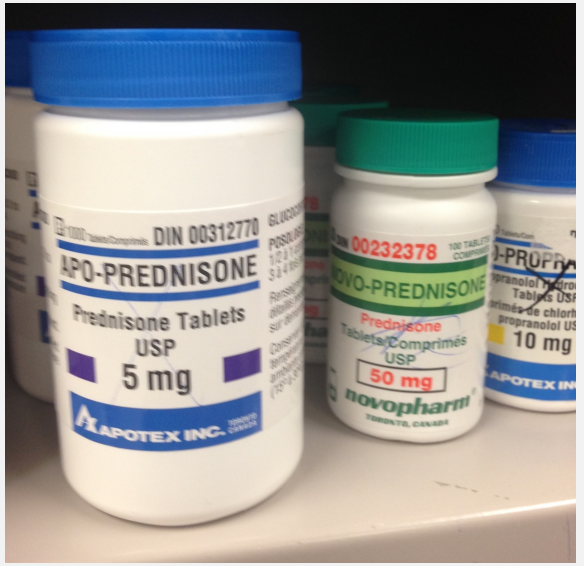
The White Knight

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

The Dark Knight

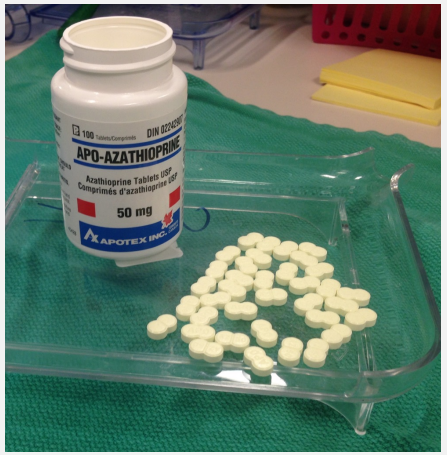
- PU/PD
- Polyphagia
- Muscle wasting/myopathy
- Collagen weakness
  - Ligament ruptures?
- GI ulceration
- Dermatological changes
  - Pot belly, calcinosis cutis
- Behavioral changes

PREDNISONE



- 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



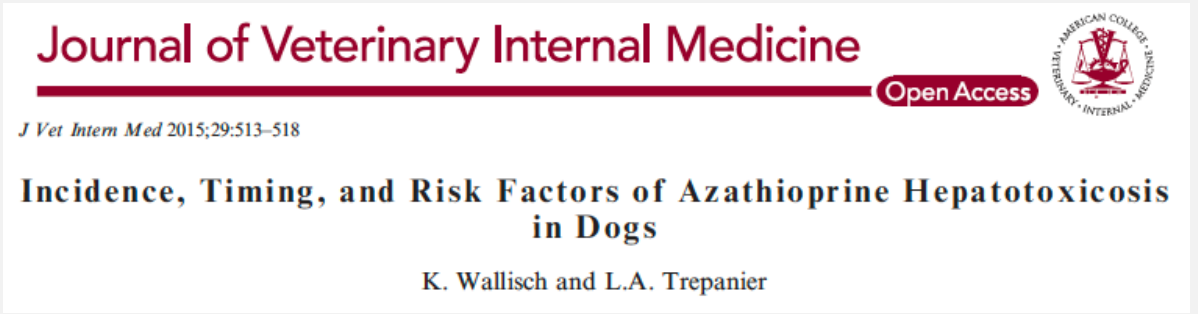
- Purine analogue antimetabolite
  - Inhibits RNA, DNA & protein synthesis resulting in decreased lymphocyte proliferation
  - Effective in 11 to14 days (NOT a fast drug)
- Immunosuppressive dose = 2mg/kg/day
  - For how long?
    - I use it daily until I wean my prednisone to a tolerable dose
    - 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 (5/34)
    - Usually occurs within 2-3 weeks in dogs, stabilized or resolves when drug is stopped
    - GSDs overrepresented

Much less common than we all fear!

- 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 Mississippe 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)
  - Thrombocytopenia – with long term usage

- 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

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

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

DNA synthesis inhibitors – decrease lymphocyte and antibody production

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 our 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; Timothy J. Scase, BVM&S, PhD, DACVP; Peter J. Cripps, BVSc, PhD; Alexander J. German, BVSc, PhD

- 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 2nd 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

Pet Food companies can be a great resource to help you select a diet !

TABLE 132-1

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 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

CUTE CAT

- 12-year-old FS DSH
- 4 months prior for vomiting and intermittent diarrhea
  - AUS noted support for pancreatitis (hypoechoic pancreas)
  - Managed supportively with fluids, buprenorphine and Cerenia
  - Still has episodes on and off, with no real response to supportive care
    - Hypoallergenic diet – he hates them
    - Prednisolone – Maybe some improvement, but owner not sure…
- 1 week prior to returning she had another episode of vomiting
- Physical Exam
  - Quite unremarkable
  - Slightly underweight (4.5kgs)

LEIF 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 - [illegible]	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
  - Duodenum very friable mucosa

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 midly 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/CE VS. SMALL CELL GI 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 Open Access

American College of Veterinary Internal Medicine

STANDARD ARTICLE

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

Kayode Garraway[1] | Chad M. Johannes[2] | Angela Bryan[3] | John Peauroi[4] | Giacomo Rossi[5] | Min Zhang[6] | Chong Wang[7] | Karin Allenspach[8] | Albert E. Jergens[9]

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 TO 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 Daniaux[1], **Michele P Laurenson**[1], **Stanley L Marks**[2], **Peter F Moore**[3], **Sandra L Taylor**[4], **Rachel X Chen**[4], and **Allison L Zwingenberger**[5]

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:

CLONALITY TESTING RESULTS

DIAGNOSIS:

Duodenum: Lymphoma, enteropathy-associated type II

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

TREATMENT OF GI SCLSA

- Prednisolone 2mg/kg/day
- Chlorambucil
  - 20mg/m^2 every 2 weeks
- Once clinical signs controlled, I begin to taped the prednisone
  - Every 2-3 weeks until I reach 1mg/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/m^2 orally once every 2 weeks. Because of client preference, two cats were switched to 20 mg/m^2 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/m^2 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?

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*

- Toxicities
  - Chlorambucil
    - GI Signs (~20-25%)
      - Vomiting, diarrhea
    - Neutropenia
      - Typically rare, mild, resolves with treatment delay
      - Thrombocytopenia
        - Occurs with chronic use and is NOT reversible
    - Hepatotoxicity
      - 10% of cats – resolves with stopping drug

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

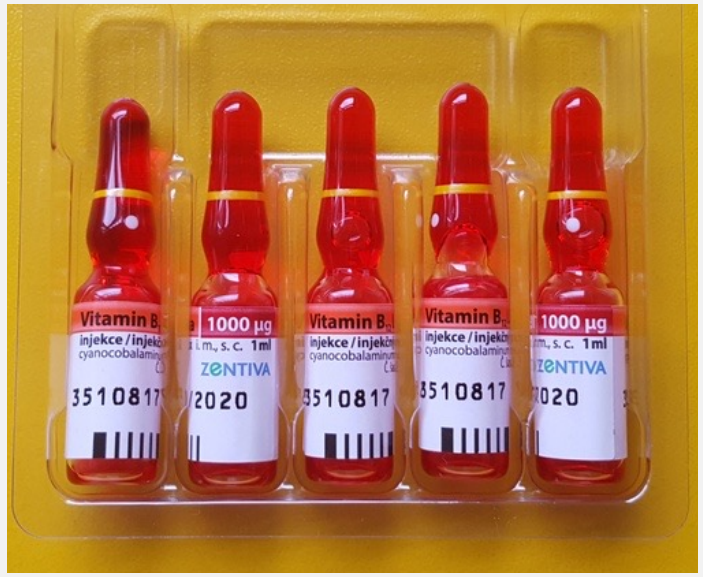
Initial response rate 86%

Median progression free survival = 1078 days!!

Dosing of chlorambucil was quite variable

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?

Short Communication

jfms Journal of Feline Medicine and Surgery

Oral cobalamin supplementation in cats with hypocobalaminaemia: a retrospective study

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

DOI: 10.1177/1098612X16689406
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SAGE

Linda Toresson[1,2], Joerg M Steiner[3], Gunilla Olmedal[2], MajBritt Larsen[2], Jan S Suchodolski[3] and Thomas Spillmann[1]

- 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

Journal of Veterinary Internal Medicine
ACVIM
Open Access

J Vet Intern Med 2016;30:101–107

Oral Cobalamin Supplementation in Dogs with Chronic Enteropathies and Hypocobalaminemia

L. Toresson, J.M. Steiner, J.S. Suchodolski, and T. Spillmann

CVMA-SBCV Chapter

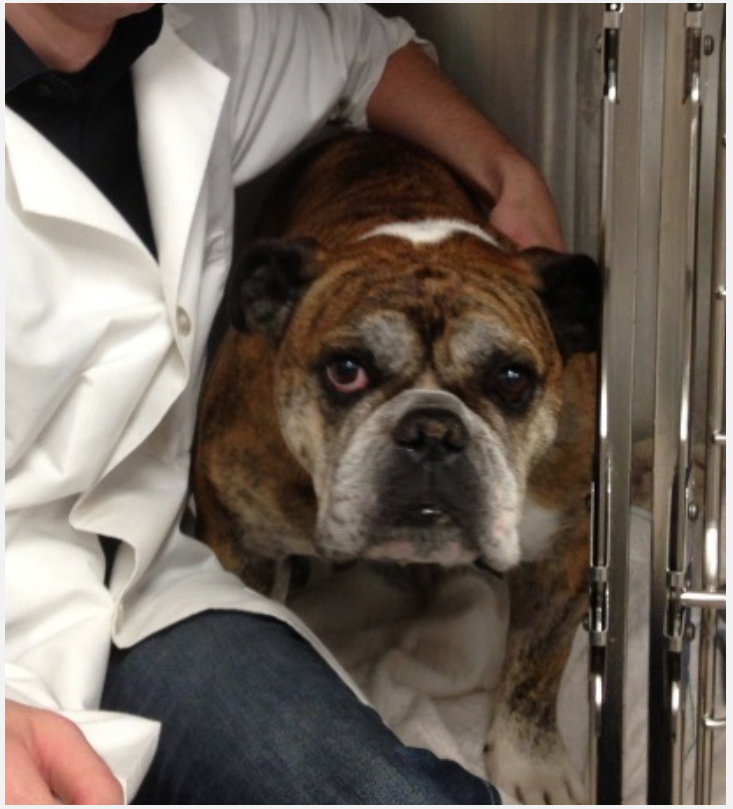
QUESTIONS?

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 large bowel diarrhea
  - Increased frequency, urgency. Mucous, tenesmus
  - No travel history, UTD on vaccines and routinely dewormed
- Diagnostics:
  - CBC – Normal
  - Biochemistry – Normal
  - UA – 1.38 USG, quiet sediment
  - Fecal float negative, Fecal PCR negative



COLITIS – DIFFERENTIAL DIAGNOSES

- 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!)

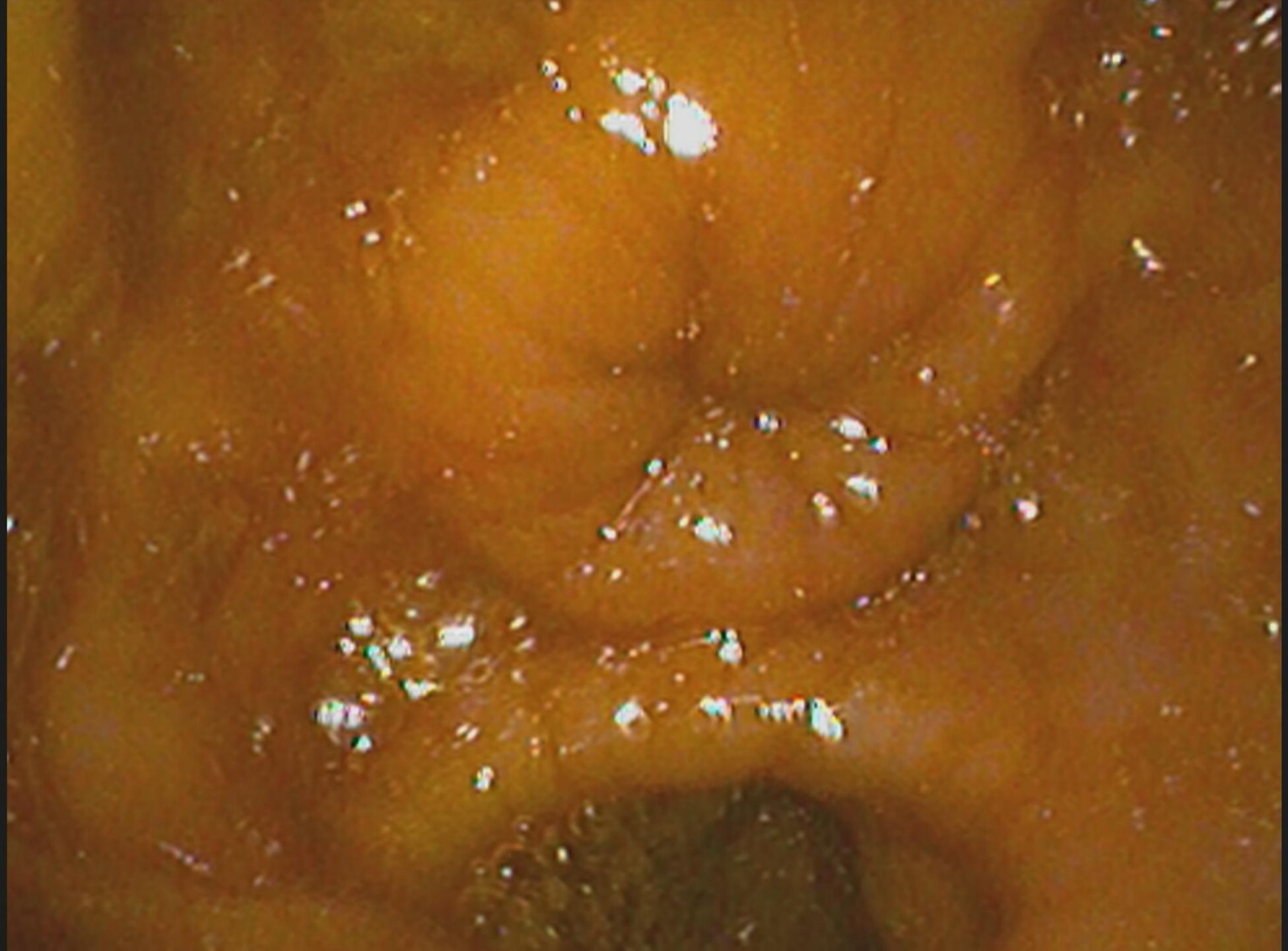
PREPARATION…

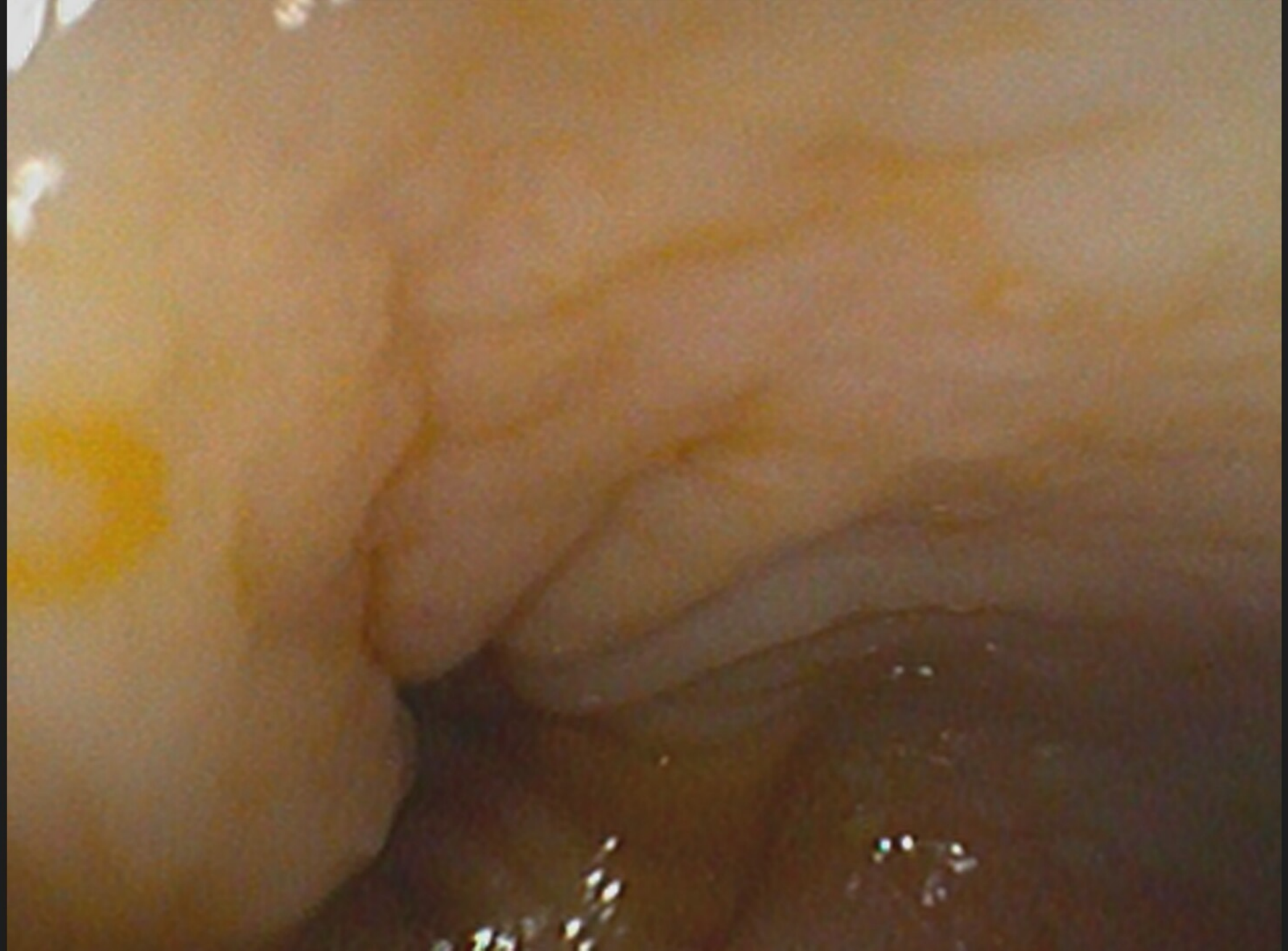
- How do we perform a colonoscopy and get adequate samples?
- Much debate over best way to prep a patient for colonoscopy
- Ideally:
  - 2 doses of PEG solution, given two hours apart via orogastric tube the evening before the procedure
  - 2 enemas the evening before the procedure
  - 1 enema the morning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

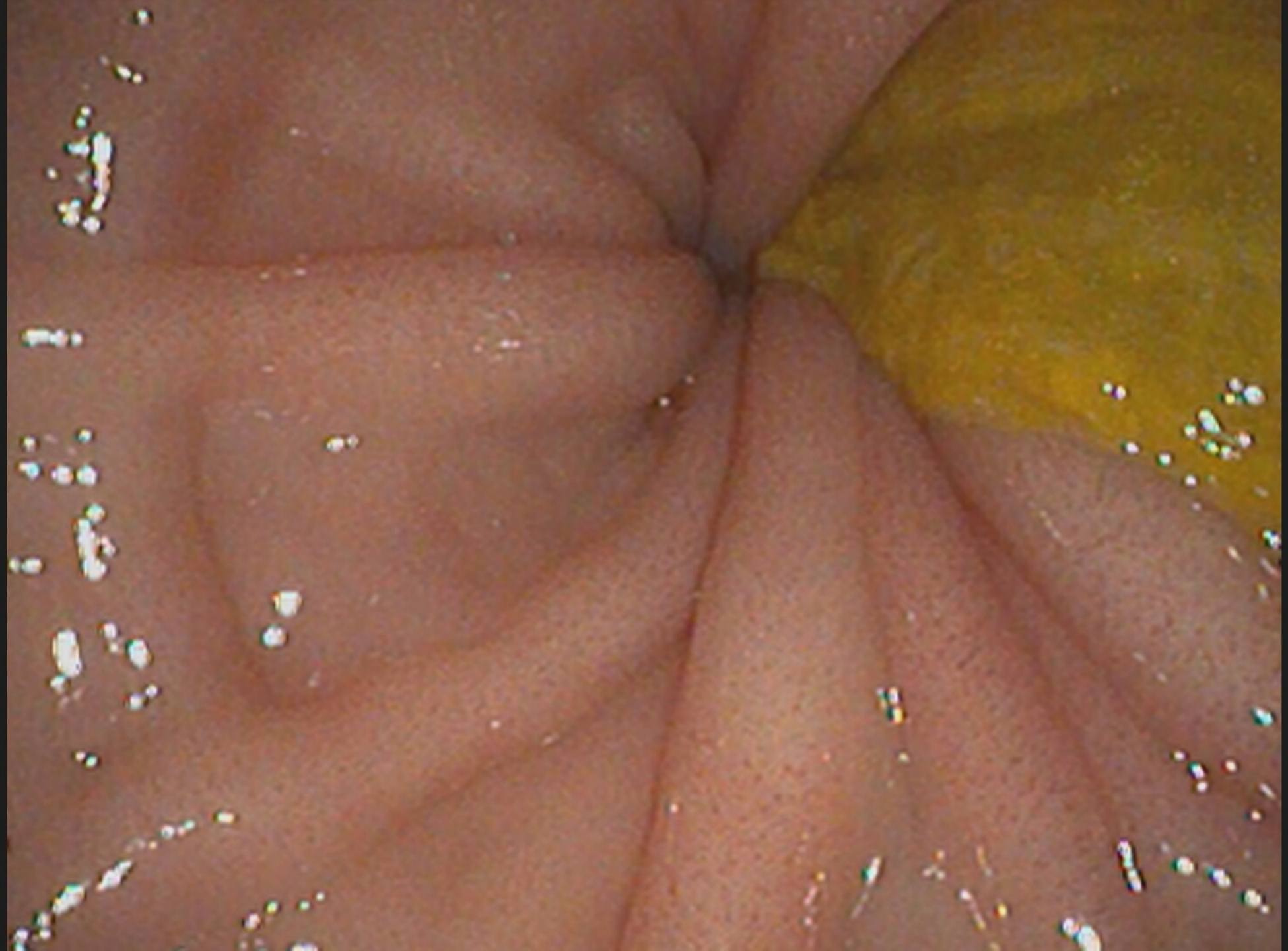
When was the last time something went "ideally" for you?

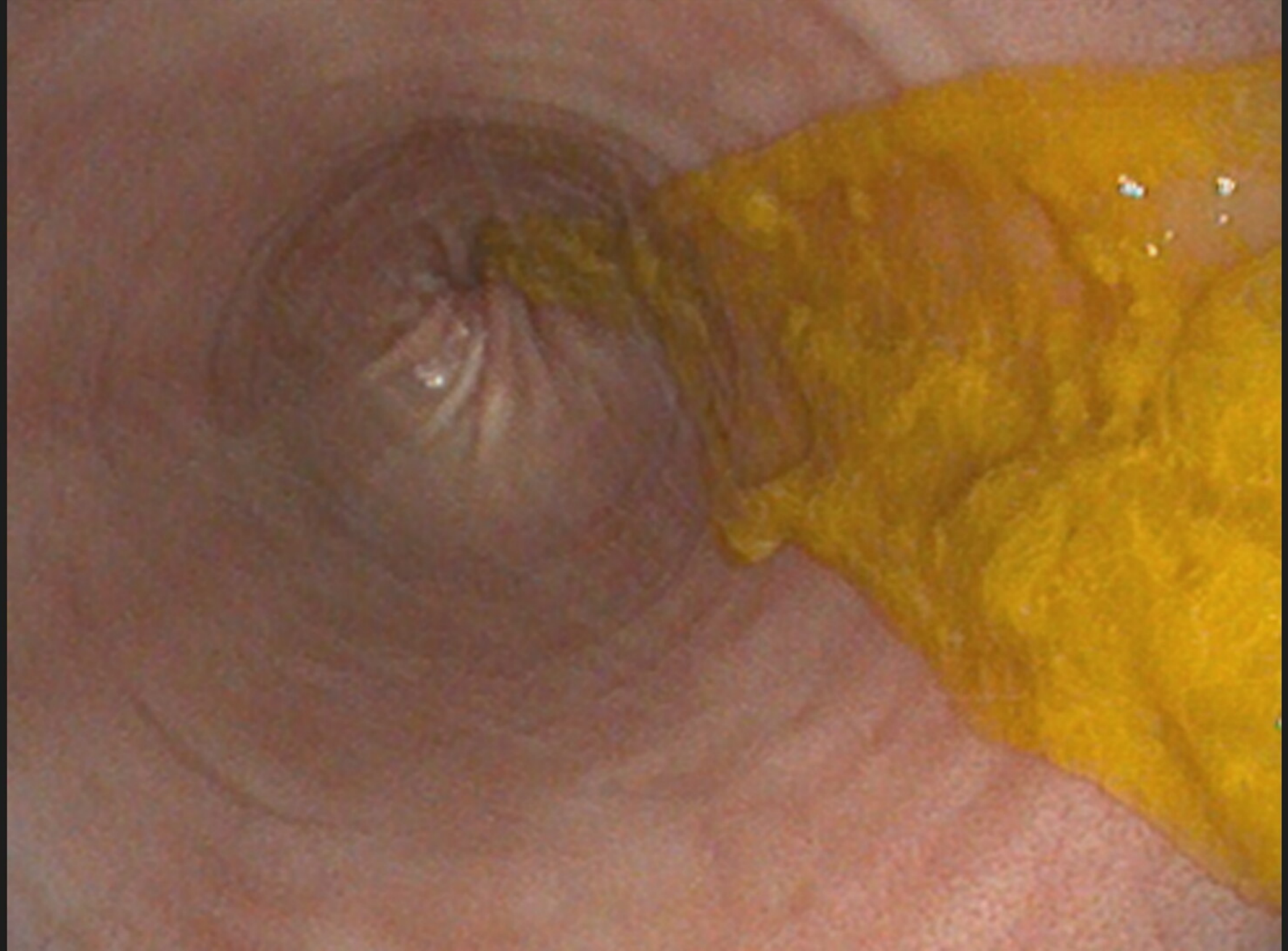
PREPARATION CONTINUED

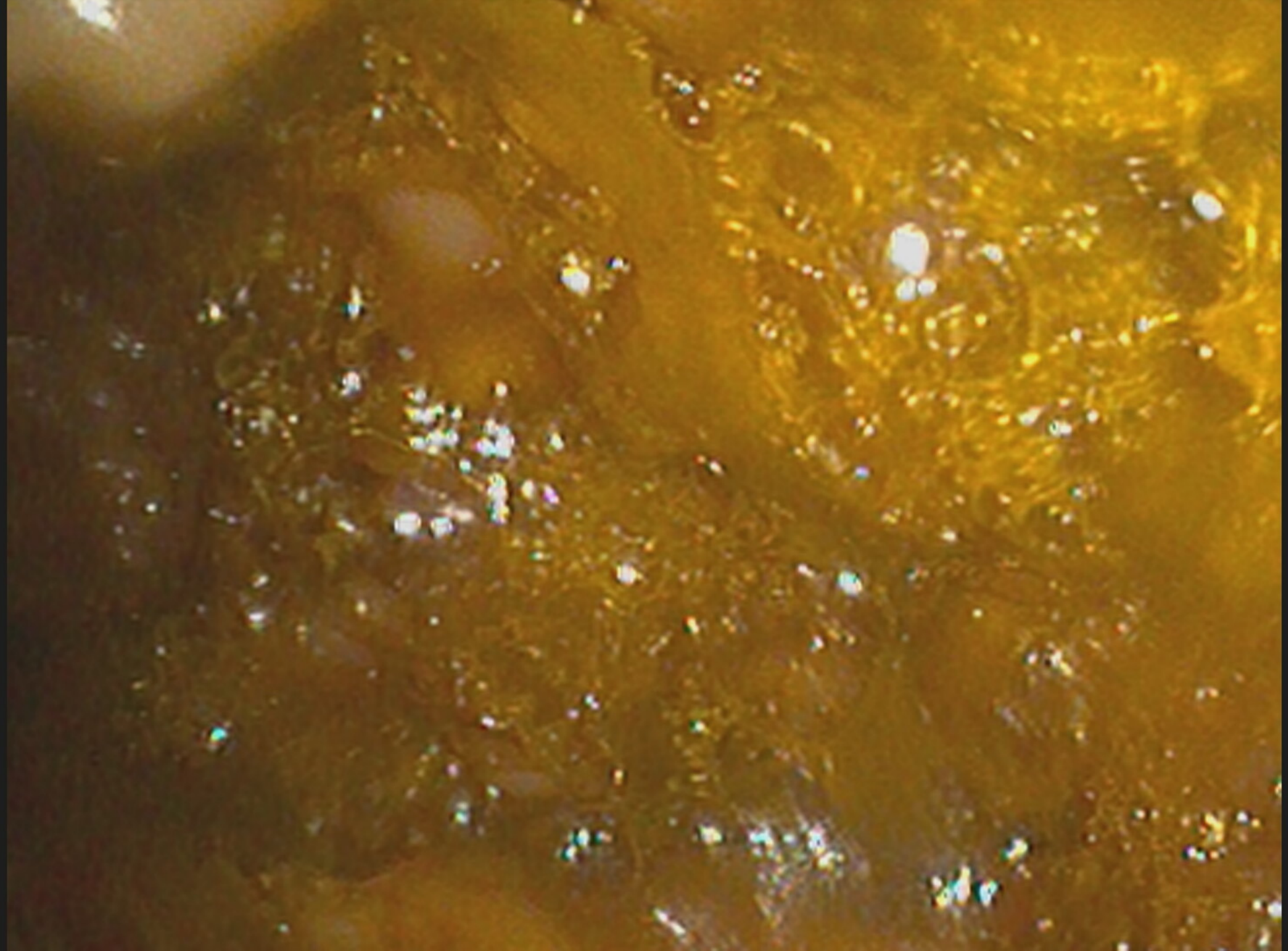
- Many many different "modified" routines
- For small dogs and cats:
  - Fasted for 24-48 hours
  - Enemas after under general anesthesia, prior to scoping
- For cats and dogs you don't want to pass an orogastric tube:
  - Place a NE or NG tube and administer a CRI of the PEG solution
  - Add on enemas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

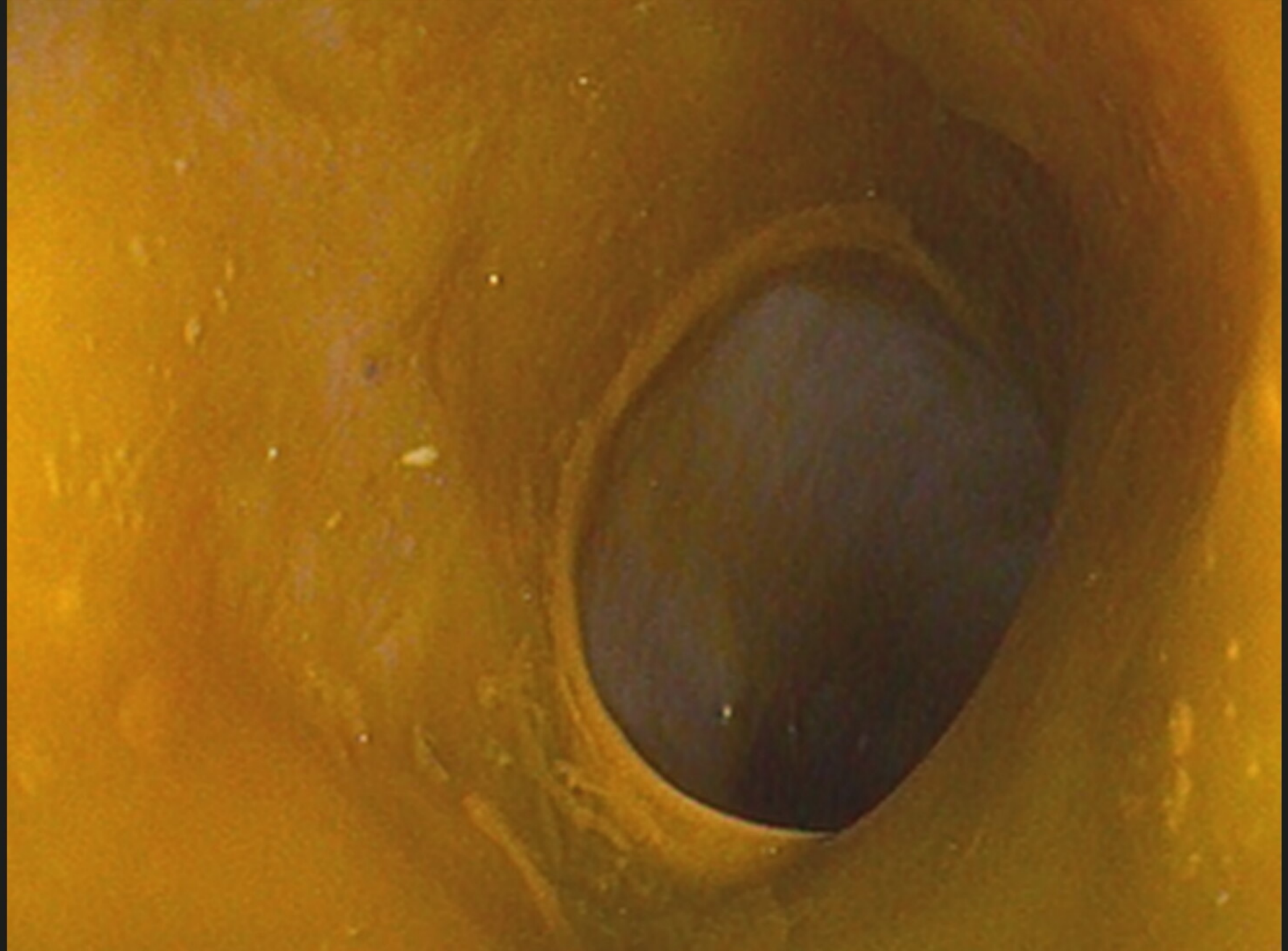












KALLIE

- 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- TREATMENT

- Options are much like we have already discussed:
  - Diet, antibiotics, immunosuppressive
- No reliable way to predict which dogs will respond to what treatment or combination of therapies
- MUST RULE OUT differentials 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 immunosuppressive therapy
  - Many owners are not super patient, 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 response
  - Easily digestible diets
    - Less material presented to colon may reduce a mount of diarrhea
  - Several studies show dogs can relapse when switched back to a "normal diet"
    - So I tend to leave them on these diets for life

FIBER RESPONSIVE LARGE BOWEL DIARRHEA

J Vet Intern Med 2000;14:27–32

Treatment of Chronic Idiopathic Large-Bowel Diarrhea in Dogs with a Highly Digestible Diet and Soluble Fiber: A Retrospective Review of 37 Cases

Michael S. Leib

- Fiber can have many effects in the GI tract
  - Improves colonic microbiome
  - Increases peristalsis (helpful in constipation)
  - Fecal bulking agent
  - Water binding
  - Bile acid binding
- Dogs that don't respond to other dietary/medical therapy
- 1g/kg/day of fiber

FIBER OPTIONS

- Psyllium (Soluble Fiber)
  - Increases viscosity of intestinal contents to resolve diarrhea
  - Slows gastric emptying
  - Increases peristalsis
- Pumpkin
- Fiber diets
  - Hill's W/d
  - RC GI Fiber response

COLITIS - TREATMENT

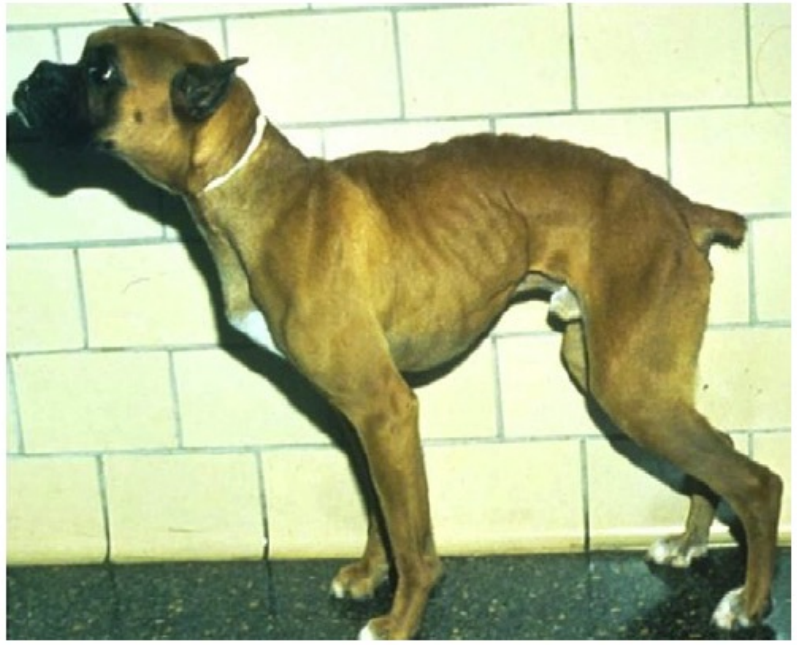
- Antibiotics
  - Metronidazole – which most of them have seen before they get to me!
  - Tylosin – as previously discussed, can be a good long-term choice
- Immunosuppressive drugs
  - Same concept as we discussed earlier. Same drug options, doses, tapering plans, etc…
- Alternative drugs
  - Sulfasalazine – 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.

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

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

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]

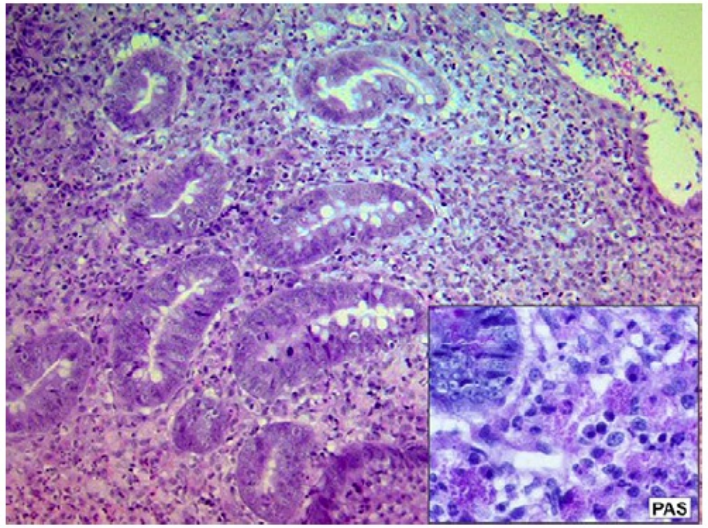


Fig. 2. GC-affected colon mucosa showing mucosal ulceration; goblet cell loss; and dense cellular infiltration with macrophages, lymphocytes, plasma cells, and eosinophils (hematoxylin-eosin, original magnification × 40). Inset: oamy macrophages positive on periodic acid–Schiff (PAS) staining, pathognomonic for GC (original magnification × 200).

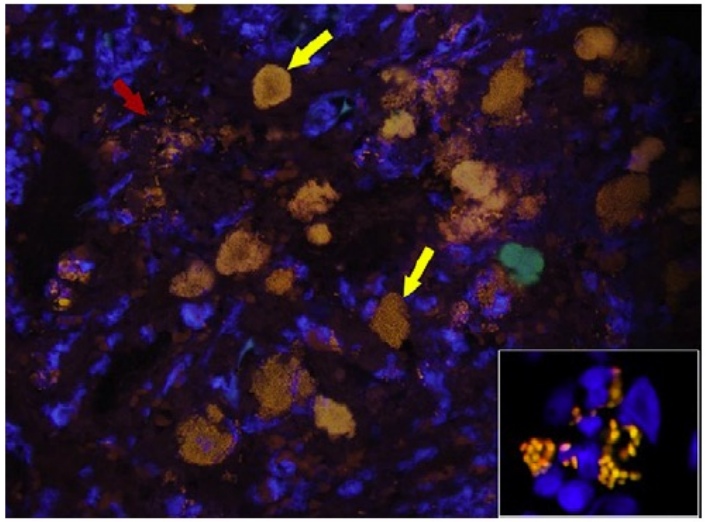


Fig. 3. FISH image (original magnification × 40) of GC colon mucosa showing typical clusters of *E coli* within the mucosa (*red arrow*) and intracellularly with macrophages (*yellow arrows*). Inset: invasive *E coli* within a macrophage. *E coli*-Cy3 probe (*red*) with non-EUB3386FAM (*green*) and 4′,6-diamidino-2-phenylindole (4′-6-diamidino-2-phenylindole [DAPI]) (nuclei in *blue*).

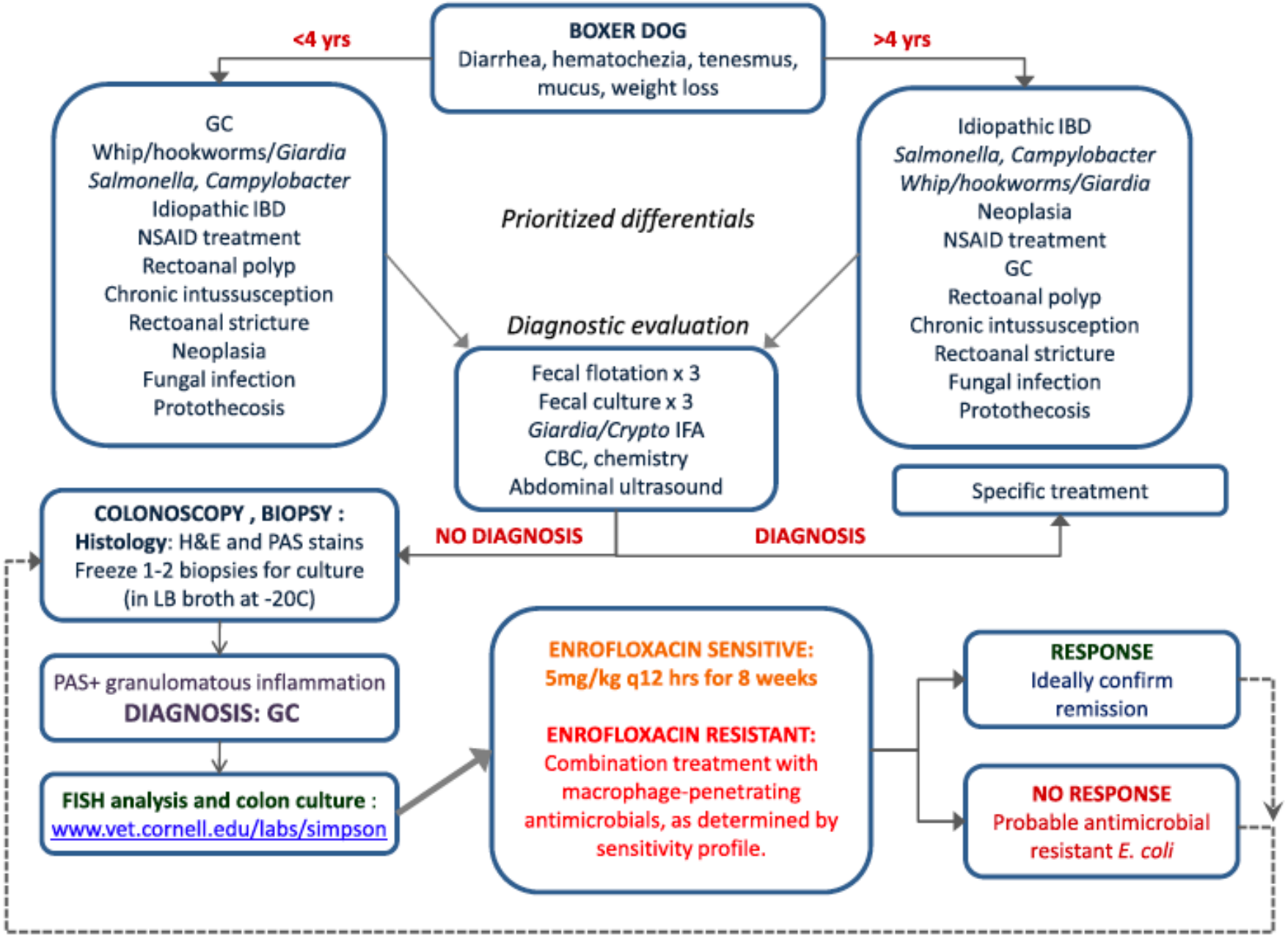
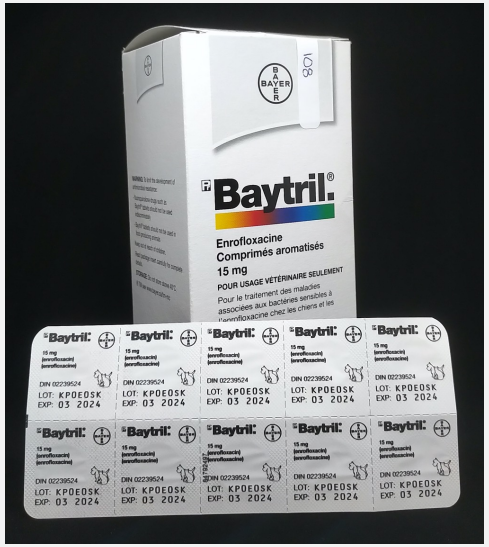
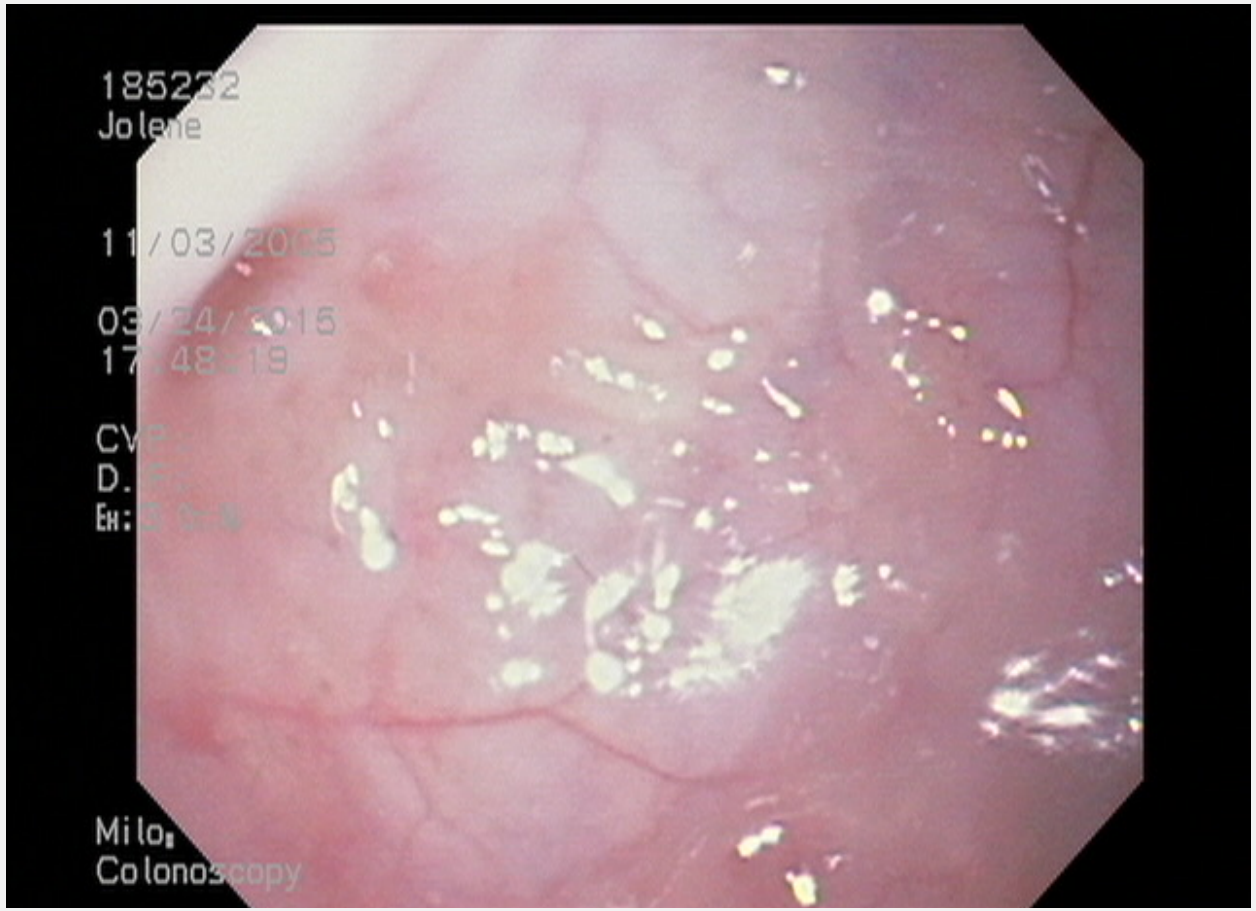


Fig. 5. Summary of the approach to diagnosis and treatment of GC. CBC, complete blood cell count; H&E, hematoxylin-eosin; IFA, immunofluorescence assay; NSAID, nonsteroidal antiinflammatory drug.

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



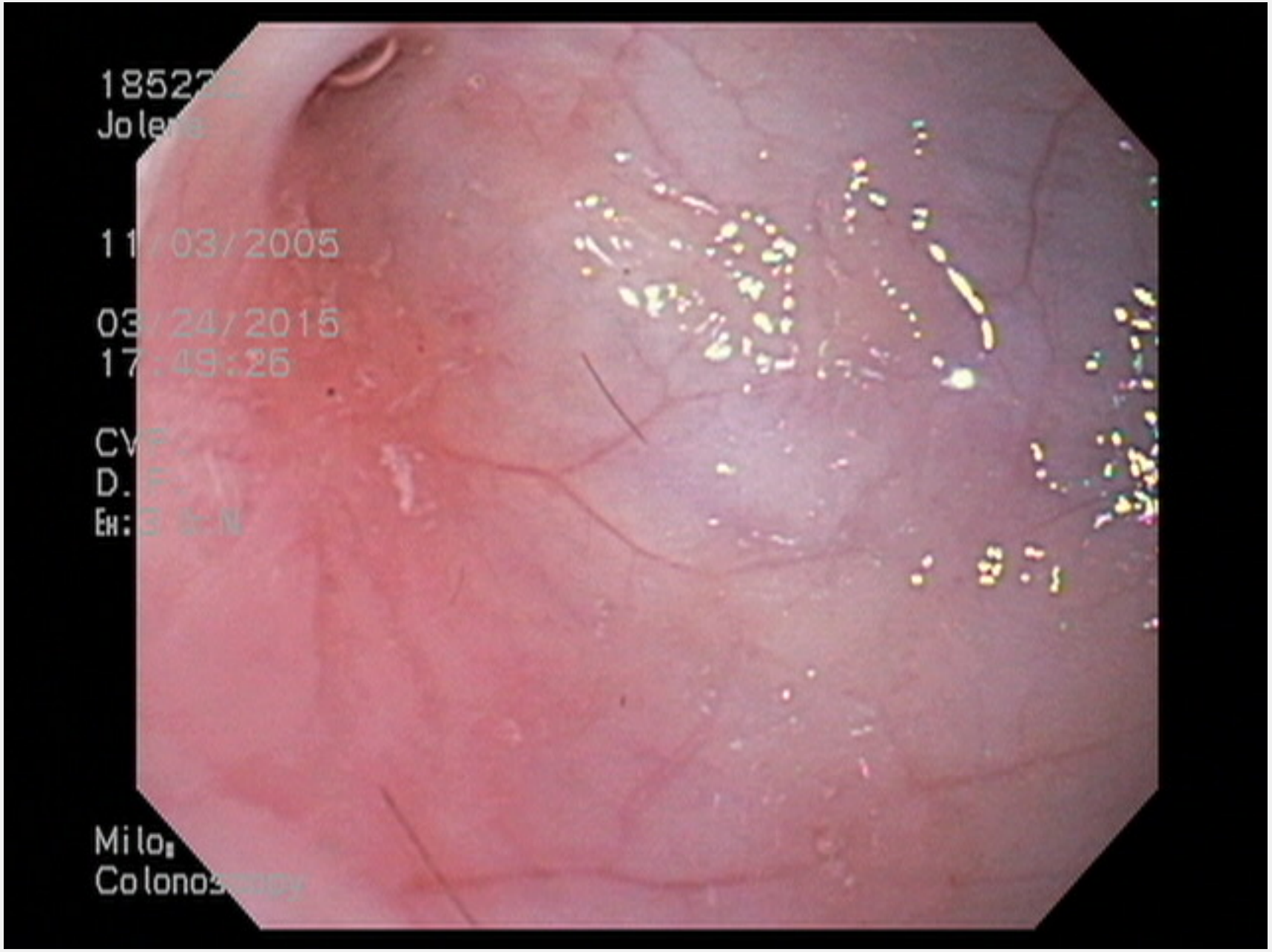


CAT COLON

Remember where LSA happens:

- Jejunum

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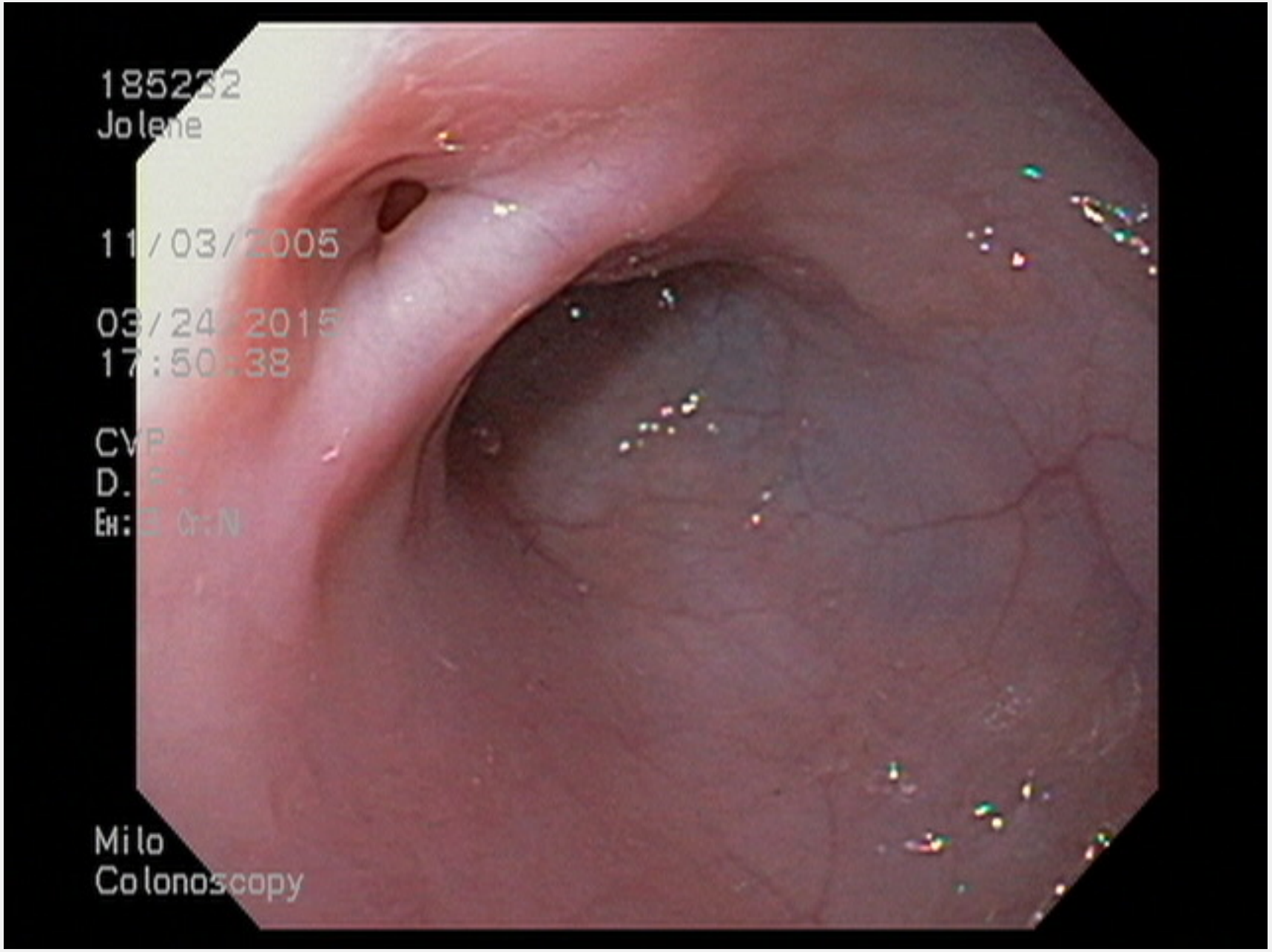
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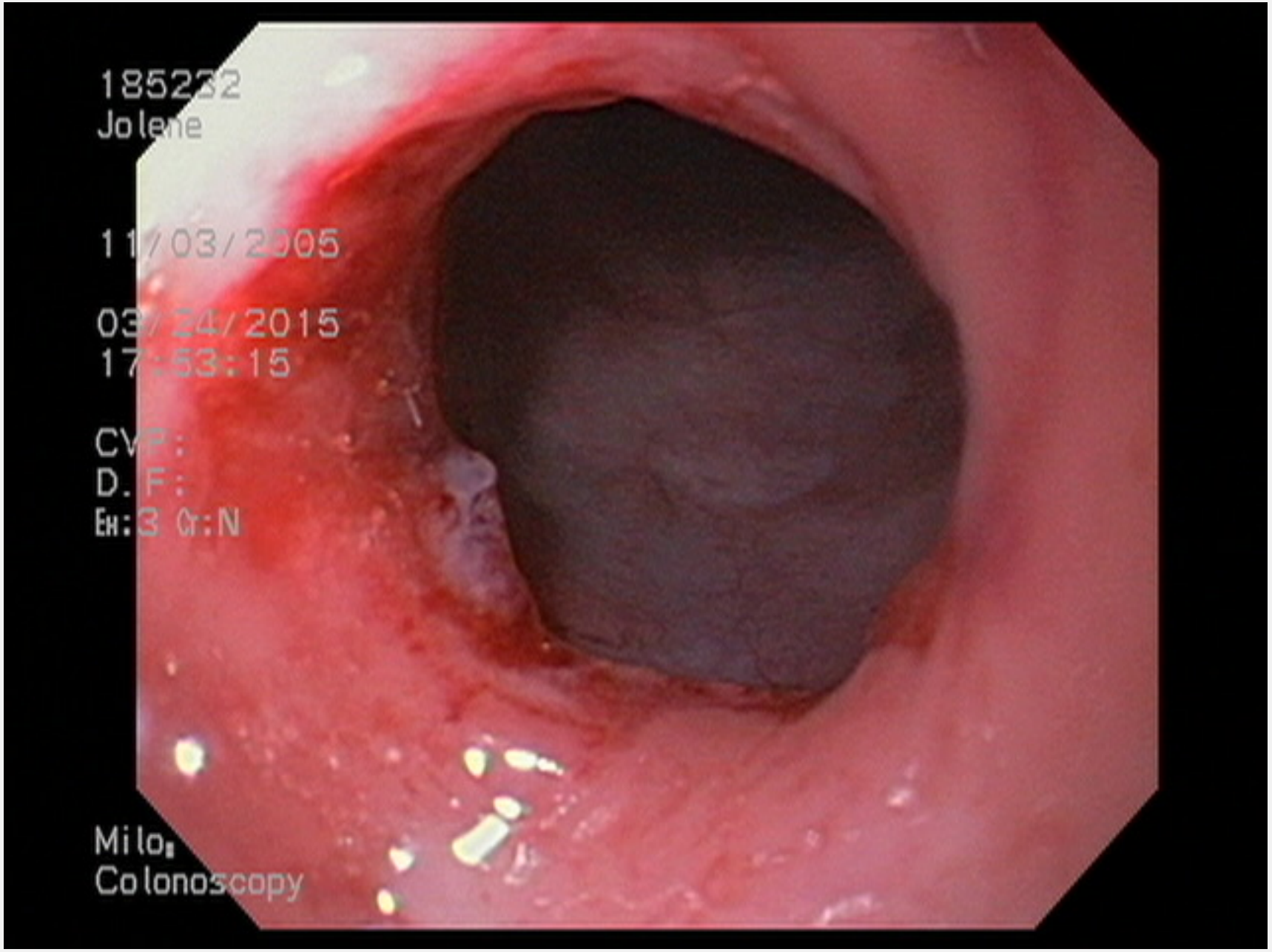
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Colonoscopy

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, can have improvement of signs
  - BUT shed or relapse for >6+ years
  - Source of infection for other cats…asymptomatic carriers

TTF DIAGNOSIS

- NC State vet school
  - 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

NC STATE T. FOETUS DIAGNOSTIC LAB

When are the tests performed?
Tests are set up once a week, typically on Monday afternoon.

When are the results available?
Results are available on Thursday or Friday each week and are emailed directly to your veterinarian.

Do I need to send payment with the sample?
No. A bill will be sent to the address provided on the submission form.

How do samples need to be shipped?
Overnight shipping is NOT necessary. If feces are placed in rubbing alcohol as we suggest, they will be stable long-term at any temperature and can be shipped by any ground carrier. Refrigeration, freezing, or overnight shipment is not necessary.

What kind of fecal sample is best?
Feces must be diarrheic. Formed samples rarely test positive even if occult infection is present.

Avoid litter contamination of the feces. If collecting a voided fecal sample, try temporarily lining the litter pan with newspaper.

Samples collected directly from the cat using a loop or colon 'flush' are best. For more details on how we perform these collections, please consult our Owner's Guide to Diagnosis and Treatment of TF Infection at JodyGookin.com.

How much feces do I need to submit?
Submit a lima-bean sized amount of fresh feces. Put the feces in a red-top vacutainer tube and then fill the rest of the tube with rubbing alcohol (isopropyl alcohol).

How long must my cat be off of antibiotics prior to testing?
Cats should not be receiving any antibiotics for at least 7 days prior to collecting the fecal sample.

How much does the test cost?
$77.00 per fecal sample when sent directly to our laboratory.

What is the difference between your PCR and one provided by another laboratory?
Our laboratory was the first to design, validate and publish a PCR test for *T. foetus* and to validate and publish the most effective way to extract DNA from cat feces.

Any proceeds from our PCR service go directly to promoting research on *T. foetus* infection.

We do not require samples to be shipped overnight or under refrigeration.

We perform exhaustive quality control steps including

- A *T. foetus* PCR test with concurrent positive and negative control samples in each run.
- A confirmatory restriction digest of positive samples to ensure sequence amplification specific to *T. foetus*

We offer personalized service and consultation to RDVMs. Each and every test result is reviewed by Dr. Gookin.

An Owners Guide To Diagnosis and Treatment of Cats Infected with *Tritrichomonas foetus*

Jody L. Gookin, DVM, Ph.D., DACVIM (Internal Medicine)
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HighgaitsPaws Abyssinians
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HELP US IN OUR FIGHT AGAINST *T. FOETUS* INFECTION!

YOU CAN MAKE A DIFFERENCE.

If you should find this Guide useful in helping you tackle *T. foetus* infection in your cattery or clinic, please consider contributing to our effort to find a safe and effective treatment for this important infection. Any sized donation will help. Make your tax-deductible donation to **STRIVE – Support for *T. foetus* Research Innovation and Veterinarian Education.**

For further information on how to contribute please go to www.JodyGookin.com

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)

NOVEL THERAPY: FECAL TRANSPLANTATION

- Transfer of feces from a healthy patient to the gut of a diseased recipient
- What's old is new again?
  - Reports from China in humans since the 4th century
  - Western Medicine
    - Reports from 1958 in patients with pseudomembranous colitis
    - More recently – *Closrtidioides difficile* infections
      - Wider exploration underway
    - Veterinary Medicine
      - Rumen transfer
      - Copraphagy in many veterinary species

CONCEPT: FECAL TRANSPLANTATION

- Increase the richness in the intestinal microbiome
- Creates less favourable conditions for growth of "bad" bacteria (CDI)
  - Provides bacteriocins, increases secondary bile acids
  - Adds bacteriophages…
- Increases mucin production
  - Improves the mucous layer lining the intestine, decreases translocation
- Increases butyrate producing bacterial species
  - Induces regulatory T cell production and IL-10 production
    - Improves mucosal immune response and decreases inflammation

FMT USE AND BENEFITS IN PEOPLE

- Treatment of choice for recurrent *Clostridioides difficile* infection
- Used, but with more limited success in:
  - IBD, Chron's disease, ulcerative colitis, colorectal cancer
- Extra-GI disease
  - Hepatic encephalopathy, psoriasis, neurological disorders, some cancers
  - Metabolic syndrome – improved insulin response
  - Autism spectrum disorder + GI signs
    - decreased GI signs and improved behavioural signs

FMT COMPLICATIONS

- More common
  - Abdominal discomfort
  - Bloating
  - Cramping
  - Diarrhea/constipation
  - Nausea/vomiting
  - Low grade fever
- Less common
  - High grade fever
  - Bacteremia
    - Sometimes with MDR bacteria
- Rare
  - Death

FMT EVIDENCE IN DOGS

- Parvovirus
  - Fecal transplant does not significantly improve survival, but increased the percentage of survivors who had resolution of diarrhea in 48 hours
  - Shortened hospitalization from a median of 6 days to a median of 3 days
  - The fecal transplant puppies were older than the placebo group
    - They might be expected to do better anyway…
  - Giardia
    - Anecdotal reports that FMT in refractory Giardia patients may make them responsive to metronidazole/fenbendazole even if they have not been before

FMT EVIDENCE IN DOGS

- Acute diarrhea
  - Does fecal transplant help resolve acute diarrhea?
    - Adult dogs with acute diarrhea and no or mild systemic signs
    - FMT given by enema once vs 7 days course of metronidazole
    - Both groups had equal fecal consistency at 7 days
      - The FMT group had firmer feces at 28 days than the antibiotic group
    - Fecal dysbiosis index
      - Normalized at day 7 and stayed normal in FMT dogs, but not in the antibiotic group
        - Unsure how to really interpret this

Fecal Microbiota Transplantation in Dogs

Jennifer Chaitman, VMD[a], Frédéric Gaschen, Dr med vet, Dr habil[b,*]

ACUTE HEMORRHAGIC DIARRHEA SYNDROME

- Multicenter, randomized, placebo-controlled study
- Dogs with 3 days of diarrhea/vomiting
- All had colonoscopy and biopsy
  - FMT or placebo done at the end of the procedure
- No difference between treatment/controls
  - Fecal scoring – acute or more chronic
  - No difference in biome (as best they can tell)

RESEARCH ARTICLE

One dog's waste is another dog's wealth: A pilot study of fecal microbiota transplantation in dogs with acute hemorrhagic diarrhea syndrome

Arnon Gal[1]*, Patrick C. Barko[1☯], Patrick J. Biggs[2,3☯], Kristene R. Gedye[2], Anne C. Midwinter[2], David A. Williams[1], Richard K. Burchell[4], Paolo Pazzi[5☯]

PLOS ONE | https://doi.org/10.1371/journal.pone.0250344 April 19, 2021

We conclude in this small pilot study FMT did not have any clinical benefit.

FMT EVIDENCE IN DOGS

- What about chronic diarrhea?
  - Current evidence is less compelling
- Likely beneficial in patients with a significant component of dysbiosis
  - How do we decide this?
    - Folate elevations
    - High levels of *Clostridium* and toxin?
    - GI Biopsies with minimal or neutrophilic inflammation?
- May need to be repeated, though how frequently is unclear

Fecal Microbiota Transplantation in Dogs

Jennifer Chaitman, VMD[a], Frédéric Gaschen, Dr med vet, Dr habil[b,*]

WHEN TO CONSIDER IN DOGS?

- After your work up – NOT before
- Find a treatable disease and treat it
  - If the response is not ideal, then consider FMT
- Current antibiotic therapy?
  - Not ideal, as this may negate the benefits
- Immunosuppressed dogs?
  - In general, IBD dogs on treatment seem not to have other side effects, so are reasonable to treat

DONOR SELECTION?

Fecal Microbiota Transplantation in Dogs

Jennifer Chaitman, VMD[a], Frédéric Gaschen, Dr med vet, Dr habil[b,*]

Vet Clin Small Anim 51 (2021) 219–233
https://doi.org/10.1016/j.cvsm.2020.09.012 .012

Box 1
Recommended selection criteria for canine fecal donors

History and physical examination
- Preferably between the ages of 1 and 10 years
- Preferably no travel history outside the local area
- No health issues in the last 6 or 12 months
- No history of chronic GI diseases, allergies, and immune-mediated diseases
- Has not received any antibiotics in the last 12 months
- Regularly vaccinated according to existing guidelines
- Fed a balanced diet
- Not overweight or underweight (9-point body condition score between 4 and 6)
- Normal fecal consistency
- Deemed healthy on physical examination

Laboratory screening
- Normal CBC and serum biochemistry
- Consider evaluation of basal cortisol, thyroxine
- Negative for parasite ovas on fecal floatation, consider empirical deworming with a broad-spectrum anthelmintic drug
- Negative for Giardia oocysts on fecal floatation and ELISA fecal test, see above for empirical deworming
- Consider testing for fecal pathogens such as *Salmonella* spp., *Campylobacter* spp., etc.

Fecal microbiome evaluation
- Fecal dysbiosis index[31] less than 0

Abbreviations: CBC, complete blood count, ELISA, enzyme-linked immunosorbent assay.

OTHER TESTING OR DIET CONSIDERATIONS?

- What about other GI diseases?
  - Intestinal Absorption
    - B12, folate
  - Endocrine testing?
    - Addison's disease – Cortisol vs ACTH stimulation
    - Thyroid testing – T4, FT4, TSH
  - Pancreatic disease?
    - TLI
    - cPLI

Bottom Line:

We don't know yet what is necessary vs what is best…

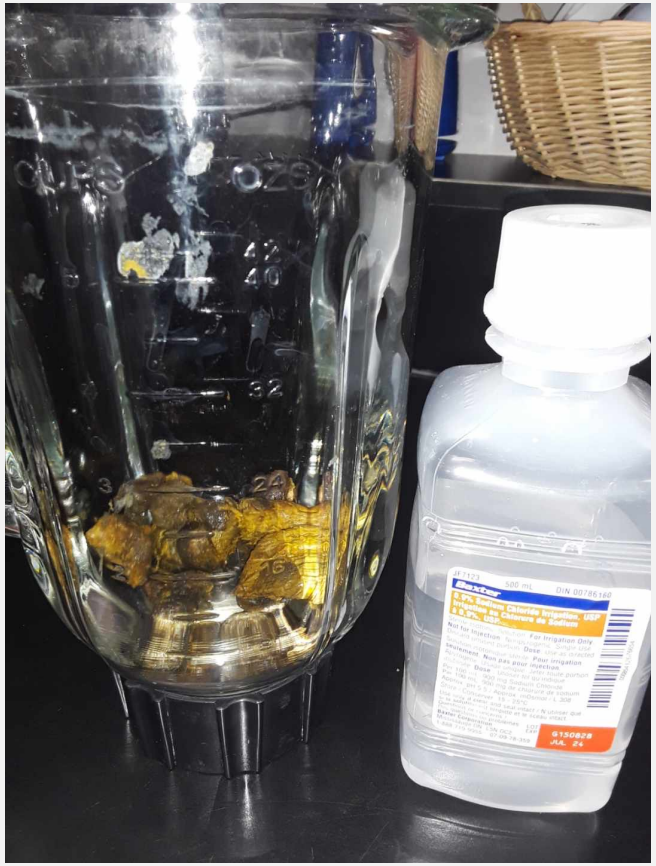
SAMPLE PREPARATION

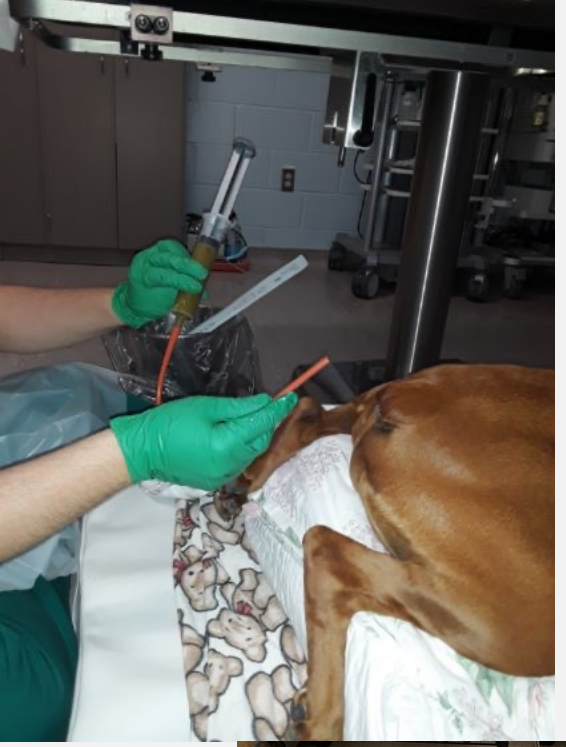
- Fresh samples
  - Use within 6 hours
  - Some evidence that can be refrigerated for a week, but longer than that is unknown
- Dose?
  - 20-100g/patient
  - 1-5g/kg of recipient patient weight

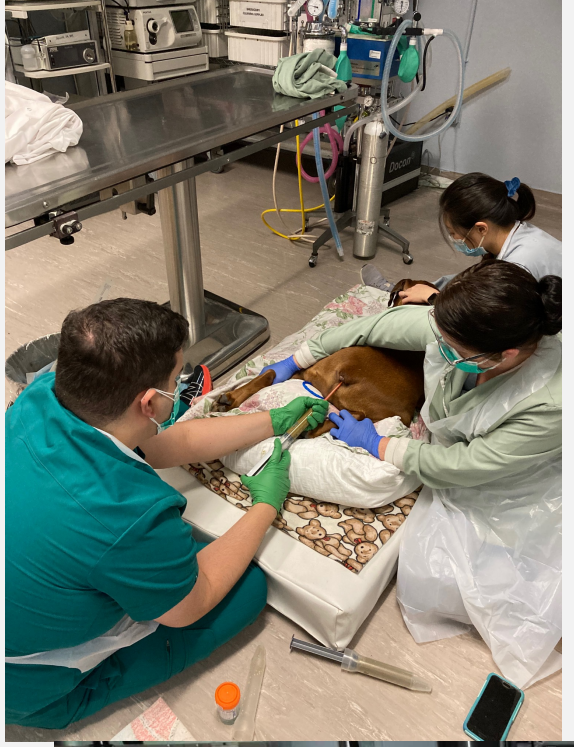
FMT ADMINISTRATION

- Available Routes:
  - Oral capsules, NG tube, colonoscopy, enemas
- Still much debate in both human and veterinary medicine
  - Humans
    - Colonoscopy and oral capsules may be better
    - Randomized controlled study found enemas to be effective
  - Veterinary
    - Enemas are the easiest, though capsules are also available

FECAL TRANSPLANT








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

www.Wikipedia.org

http://shepherdshoperescue.org

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 < 8.0ug/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 our 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 (B12)

- 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 fiber, 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
  - I feel 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; important to check!

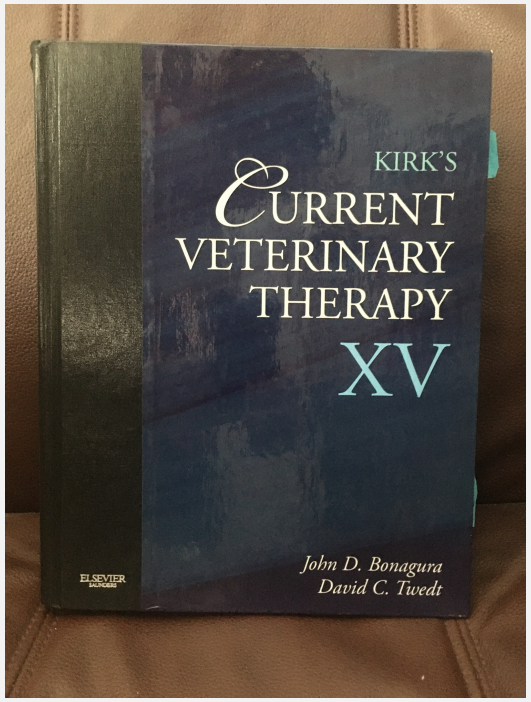
EPI AND CATS

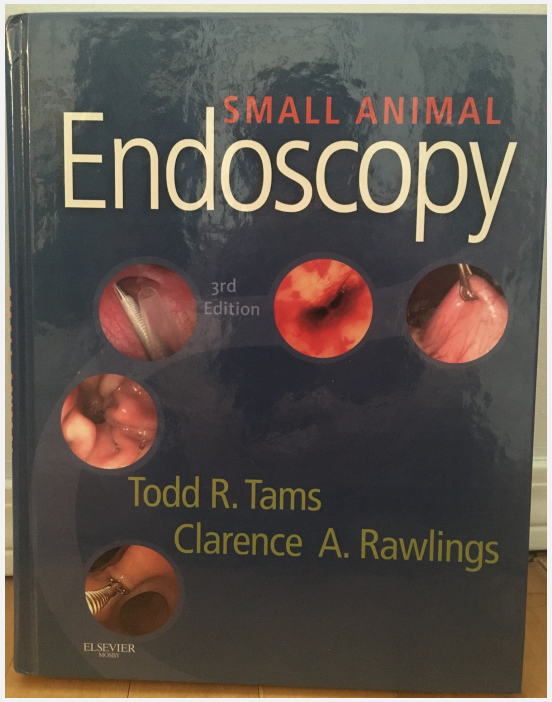
- Looks like a lot of other cat diseases!
- Polyphagia and weight loss
  - EPI
  - Hyperthyroidism
  - DM
  - Early CKD
  - GI lymphoma
- Old cats often have more than one thing going on at a time…
  - So remember to look!

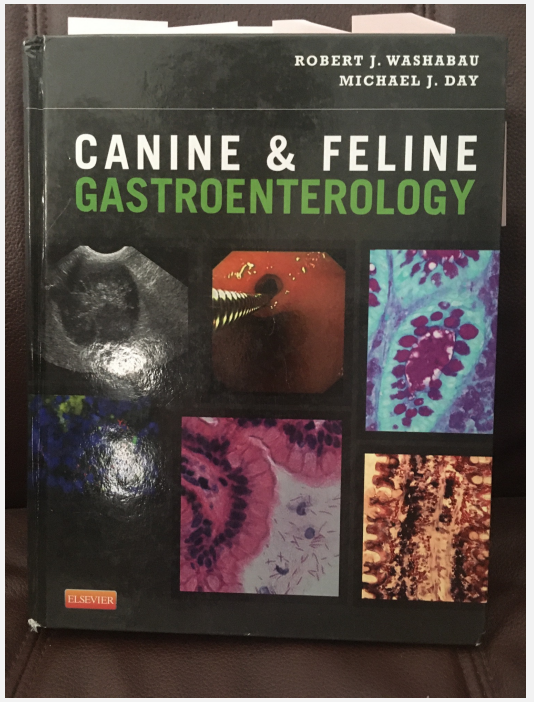
Best Internal Medicine differential ever!

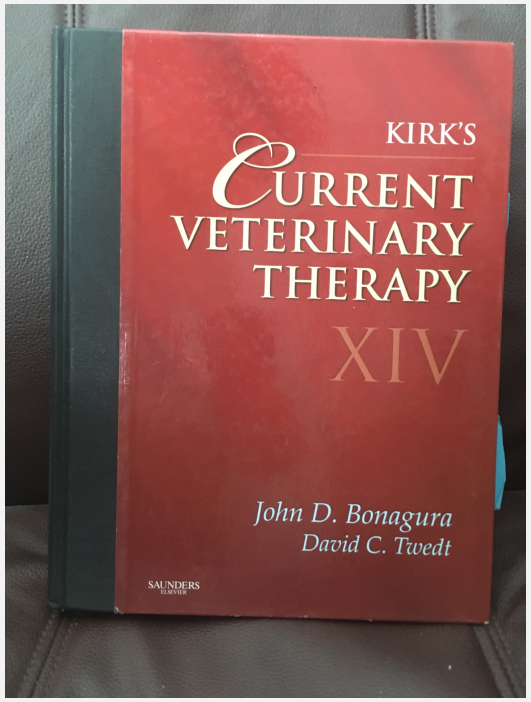
CAT EPI TREATMENT

- 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
- Cobalamin
  - 250 ug/cat SC weekly for 4-6 weeks, guided by serum measurements









GOOD REFERENCES TO HAVE

QUESTIONS?

Thank you to the SBCV for the invitation to speak and to all of you for listening