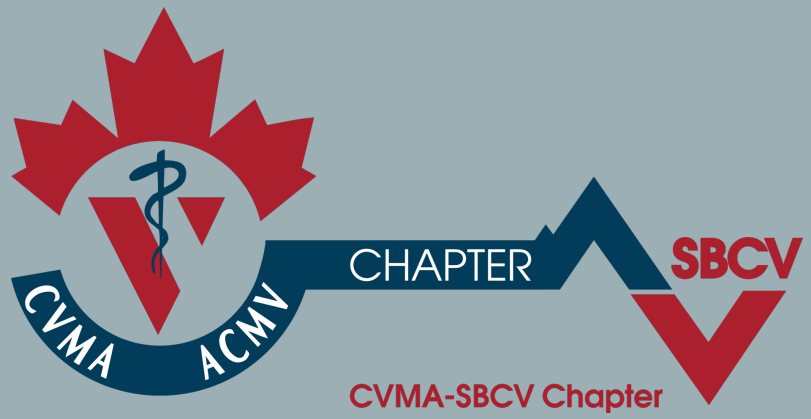


DIARRHEA IN SMALL ANIMALS

M. Casey Gaunt, DVM, MVetSc, DACVIM (SAIM)

Joe Rubin, DVM, PhD

PLAN FOR THE DAY

- Learn the Lingo
- Localization
- Acute Diarrhea
  - Special Cases
  - Infectious Organisms
- Chronic Enteropathy (IBD)
- Immunosuppression
- Large Intestinal Disease
- Fecal Transplants
- Weird and Wonderful Examples

CVMA ACMV CHAPTER SBCV
CVMA-SBCV Chapter

WHAT IS DIARRHEA?

Fecal Scoring Chart

PURINA PRO PLAN VETERINARY DIETS

SCORE	SPECIMEN EXAMPLE	CHARACTERISTICS
1		• 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		• Firm, but not hard, pliable • Segmented in appearance • Little or no residue on ground when picked up
3		• Log shaped, moist surface • Little or no segmentation • Leaves residue on ground, but holds form when picked up
4		• Very moist and soggy • Log shaped • Leaves residue on ground and loses form when picked up
5		• Very moist, but has a distinct shape • Present in piles rather than logs • Leaves residue on ground and loses form when picked up
6		• Has texture, but no defined shape • Present as piles or spots • Leaves residue on ground when picked up
7		• Watery • No texture • Present in flat puddles

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

ALL DIARRHEA IS NOT EQUAL…

Acute

- Duration of < 2 weeks

Chronic

- Duration of >2 weeks

Acute Self-limiting

- Resolves on its own in a few days
- Supportive care at home or outpatient care

Acute Life Threatening

- Requires hospitalization and more aggressive care

ACUTE DIARRHEA

Supportive Care

- Withhold food for 12-24 hours
- Bland, easily digestible diet

Empirical therapy

- Deworming
  - Appropriate for region and lifestyle
- Treatment?
  - Metronidazole…
  - Probiotics…

CHRONIC DIARRHEA

This is where IM specialists help!

Time to start running tests!

- After routine/empiric measures have failed
  - Patients ready for next line of diagnostics
- Clients usually more motivated to find an answer
  - Costs become justifiable
- 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 LOCALIZE?

Differential Diagnoses

- Some specific to a region
  - Parasitism
  - Neoplastic disease
    - i.e. polyps
  - Digestion/absorption
    - i.e. EPI

Diagnostics

- How to collect samples
  - Endoscopy
  - Surgery

Treatments

- Drugs
  - Which go where?
  - Special formulation?
- Diets
  - Hypoallergenic
  - Highly digestible

ACUTE DIFFERENTIALS

- Dietary Indiscretion
  - Food Change
  - Garbage/new food ingestion
  - Toxin Ingestion
  - Drugs
- Obstructive disease
  - FB
  - Mass
  - Intussusception
- Infectious
  - Bacterial
  - Viral
  - Parasitic/protozoal
  - Fungal
- Idiopathic/Unknown trigger
- Stress
- Environmental changes

INFECTIOUS CAUSES - OTHER

- Parasitic
  - Roundworms, hookworms, whipworms, coccidia
- Protozoal
  - Giardia, TTF
- Bacterial
  - Campylobacter
  - Salmonella
  - E. coli (wide variation here)
  - Clostridium
- Viral
  - Parvovirus
  - Coronavirus
  - Distemper virus
- Fungal
  - Histoplasmosis
  - Highly location dependent…

Acute Hemorrhagic Diarrhea Syndrome in Dogs

Stefan Unterer, DVM, Dr med vet, Dr habil*, Kathrin Busch, DVM, Dr med vet

- Severe onset of bloody diarrhea, often with vomiting
  - Marked fluid loss via intestine results in hypovolemia
- Cause:
  - Unknown, must rule out other causes of acute diarrhea
- Outcome:
  - Mortality can be high without aggressive supportive care, but <10% mortality in dogs that are hospitalized
  - Signs typically resolve with 24-72 hours of care
  - 30% of dogs can go on to develop chronic diarrhea in the future

Vet Clin Small Anim 51 (2021) 79–92
https://doi.org/10.1016/j.cvsm.2020.09.007

Acute Hemorrhagic Diarrhea Syndrome in Dogs

Stefan Unterer, DVM, Dr med vet, Dr habil*, Kathrin Busch, DVM, Dr med vet

- Diagnosis
  - Based on clinical signs
  - *Clostridium* often present in large number, but this is not specific
  - *Clostridium* enterotoxin often identified, but again, not specific
  - Hemoconcentration
    - PCV can vary widely, but often >50-60%
    - Hypoproteinemia can often be present
  - Rule out other causes of diarrhea
    - Blood work, fecal, parvo test, baseline cortisol, etc…

Acute Hemorrhagic Diarrhea Syndrome in Dogs

Stefan Unterer, DVM, Dr med vet, Dr habil*, Kathrin Busch, DVM, Dr med vet

- Treatment
  - IV fluid therapy – THIS IS THE MOST IMPORTANT THING
    - Early on, they may not even seem that dehydrated…
  - Antibiotics
    - Multiple studies have shown there to be NO benefit to the use of antibiotics in dogs with AHDS
    - *Unless* there is evidence of bacterial translocation and concern for sepsis
      - Neutrophil counts >25,000 or <3,000 for example
      - Hypoglycemia
      - Severe hypotension

AHDS POINTS OF INTEREST

- 30% of dogs may develop chronic diarrhea after
  - Thought to be due to breakdown of gut barrier and sensitization to gut bacteria
  - 42% of parvo puppies
- Early enteral nutrition may help repair gut barrier
  - Glutamine containing because enterocytes nourished from the luminal side
- Drugs that *may* impair gut barrier might make this worse
  - NSAIDS, PPIs, antibiotics that cause dysbiosis
- Probiotics
  - In people, certain probiotics *may* lessen sensitization in similar scenarios
  - Need more info in dogs to know if this is true

EMPIRICAL TREATMENT FOR ACUTE DIARRHEA

- Diet
  - Highly digestible, low fat
    - RX diets
    - Home cooked (rice/chicken/ground beef)
  - Small amounts
  - Gradual reintroduction of normal diet
- Probiotics?
  - May shorten the duration of diarrhea

METRONIDAZOLE

- Nitroimidazole antibiotic
  - Broad spectrum of activity against anaerobic bacteria
    - Including *Clostridium* and some protozoal organism like giardia
  - Immunomodulatory and anti-inflammatory effects
    - Often the rational to use in GI disease
  - Risks?
    - Neurological side effects (often at high doses, but not for everyone…)
    - Increased risk of cancer in people (banned in food animals)
    - Antimicrobial stewardship concerns

Received: 9 August 2019 | Accepted: 10 November 2019

DOI: 10.1111/jvim.15664

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

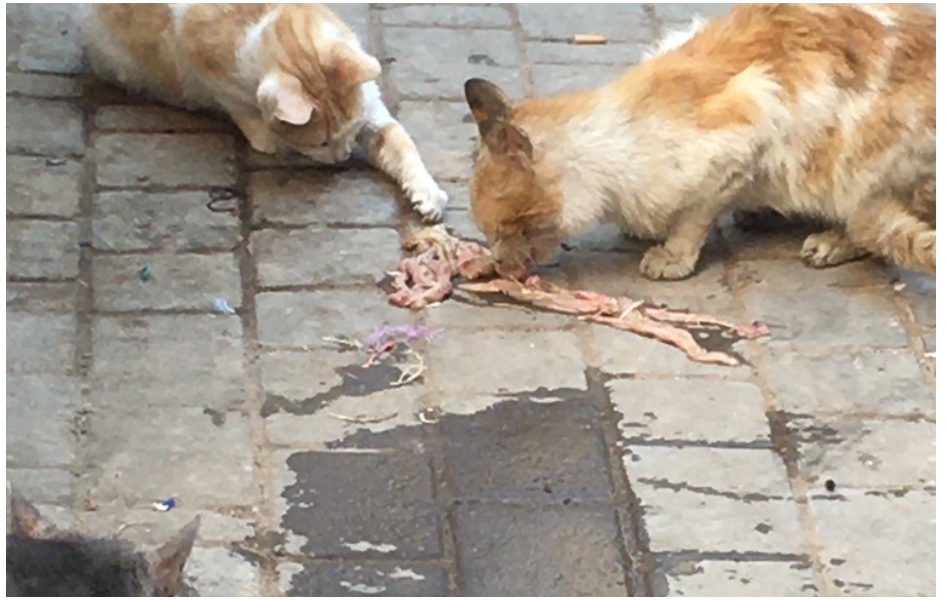
Metronidazole treatment of acute diarrhea in dogs: A randomized double blinded placebo-controlled clinical trial

Daniel K. Langlois[1] | Amy M. Koenigshof[1] | Rinosh Mani[2]

- Shortened duration of signs by 1.5 days
  - Modest improvement over placebo
  - Most dogs resolve on their own in 5-7 days
- No significant side effects reported
- Not on label for dogs
- Changes the microbiome dramatically
  - Not sure what to do with this info…

RAW FOOD

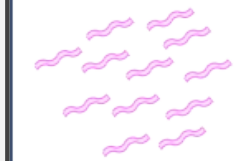
- Hugely popular
  - WHY?!?!
    - Humans learned to cook food to *increase* digestibility and improve nutrient absorption!!
- Often contains poultry
- Increases risk of exposure to food borne disease
- So why does it "work" for some dogs….



These are NOT the same thing!

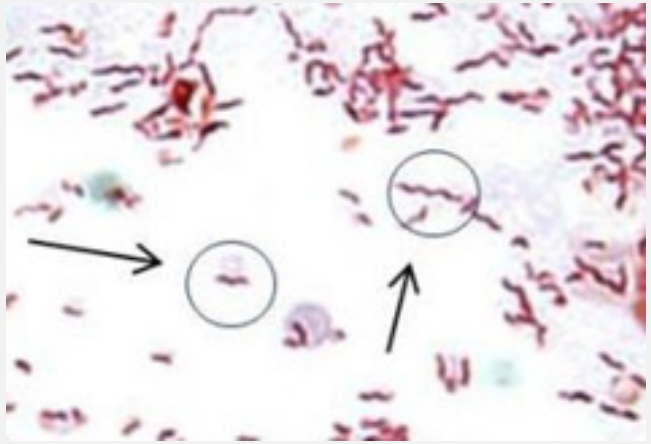
RAW FOOD – WHAT I TELL OWNERS

- If your dog is perfectly healthy, then I don't care what you feed it
  - There are still risks:
    - Carrying/shedding bacteria with zoonotic potential
    - Particularly if there are children or immunocompromised people in the household
- If your dog is sick:
  - Decreased gut barrier MAY increase risk of bacterial translocation
    - With all chronic GI disease!
  - Immunosuppressed
    - From treatment (i.e. steroids)
    - Chemotherapy



CAMPYLOBACTER

- Gram-negative ‘curvy’ organisms
  - *Campylobacter* – curved, comma or “seagull” shaped
- *Campylobacter* a challenge to grow
  - Microaerophilic
  - Requires nutritious media (blood containing)
  - Some grow at elevated temperatures, 42°C



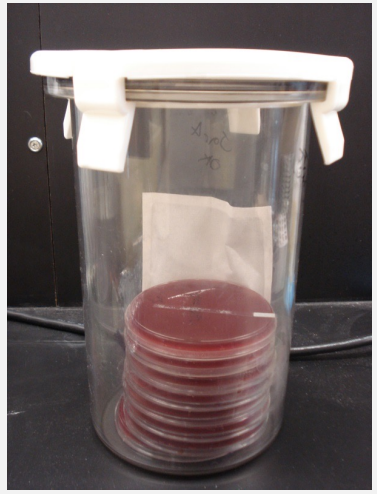
Campylobacter Gram-stain. Note the variable morphology (how many ‘squiggles’).

CLINICAL SIGNIFICANCE

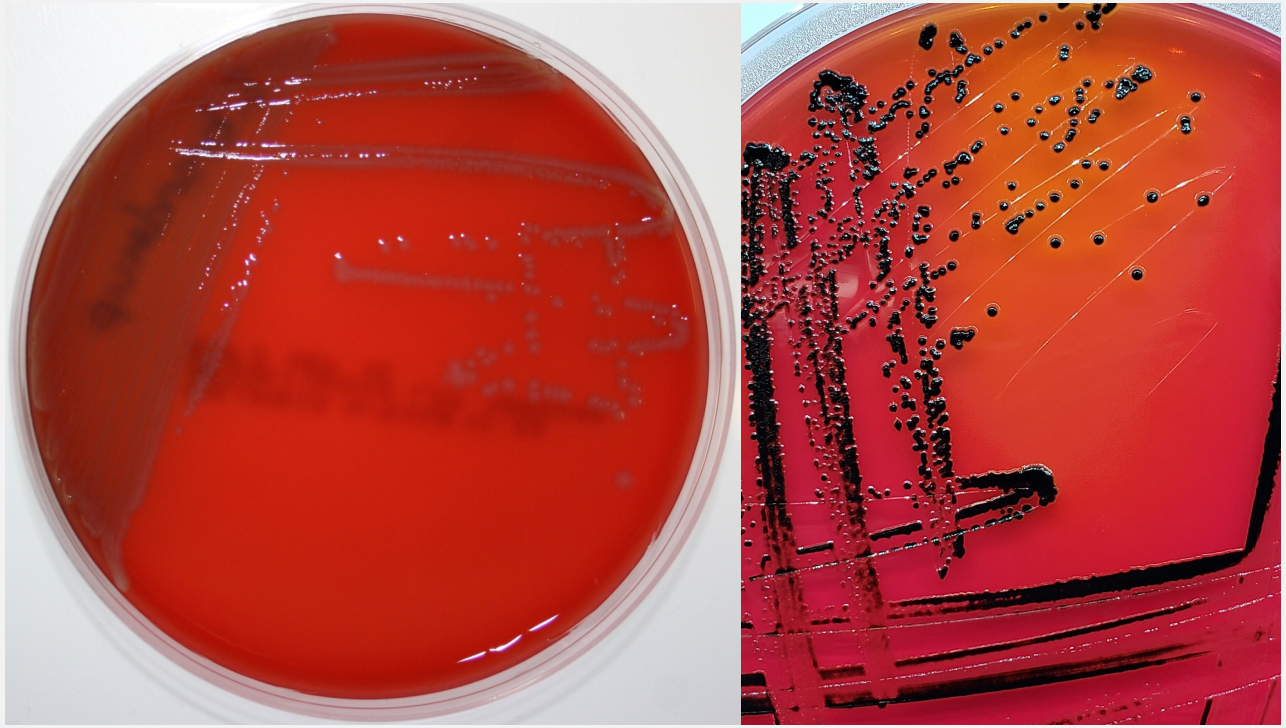
- **Take positive fecal cultures with a big grain of salt**
- Commonly isolated from healthy animals
  - **RAW POULTRY!**
  - May be associated with clinical disease in young animals <6 months
  - *Campylobacter jejuni, coli* and *upsaliensis* are the primary relevant species for companion animal health
- Disease is often self-limiting (as in people)
  - May use antimicrobials if high fever, bloody diarrhea
- May serve as household reservoir of these organisms resulting in human infections

LABORATORY IDENTIFICATION

- *Campylobacter* culture required methods
  - Extended culture periods (>48 hours may be necessary)
  - Specific atmospheres, specialized gas packs
  - Placing filter paper on agar plates that the *Campylobacter* have to swim through
- Make sure to tell lab this is what you're looking for!
- No breakpoints for susceptibility testing!
  - For *Campylobacter* or any other intestinal infection.



SALMONELLA



Salmonella on blood agar (L), and XLT-4 (R). The black colonies on XLT-4 indicate H_2S production.

SALMONELLA HOST/HABITAT

- These organisms are normal members of the intestinal microbiota of a wide variety of animals
- **RAW POULTRY!**
- *Salmonella enterica* subsp. *arizonae* associated with reptiles
- In Canada, the serotypes of *Salmonella* identified from agricultural animals varies across the country
- In Canada, *Salmonella* Enteritidis and Heidelberg are the two most common serotypes identified in human clinical disease

SALMONELLA TAXONOMY

- The nomenclature of *Salmonella* is complicated and confusing!
- Numerous taxonomic changes since the late 1980s
  - 3 species with standing in nomenclature
    - *S. bongori*
    - *S. enterica*
    - *S. subterranea* (despite the name this is not actually belong to the genus *Salmonella* – closely related to *Escherichia hermannii*)

6 Subspecies within *S. enterica*

- subsp. *enterica*
- subsp. *arizonae*
- subsp. *diarizonae*
- subsp. *houtenae*
- subsp. *indica*
- subsp. *salamae*

SALMONELLA TAXONOMY

- *Salmonella* also grouped into serovars – currently over 2,500!
- Serotyping only done by reference labs… not routine diagnostic
- Serovars are defined by the presence of surface antigens
  - O-antigens – based on the oligosaccharides associated with LPS
  - H-antigens – based on flagellar proteins
    - Can have two phases (express multiple flagellar proteins)
    - Strains may be mono- or di-phasic

Submission #	Project	Isolation #	Received	Serotype	Antigens	Phagetype	Priority / Comments
SA20156356	R	BR040E2-a	2015-10-15	POONA	22:z:1,6		
SA20156357	R	BR041E2-a	2015-10-15	URBANA	30:b:e,n,x		
SA20156358	R	BR042E2-a	2015-10-15	WELTEVREDEN	10:r:z6		

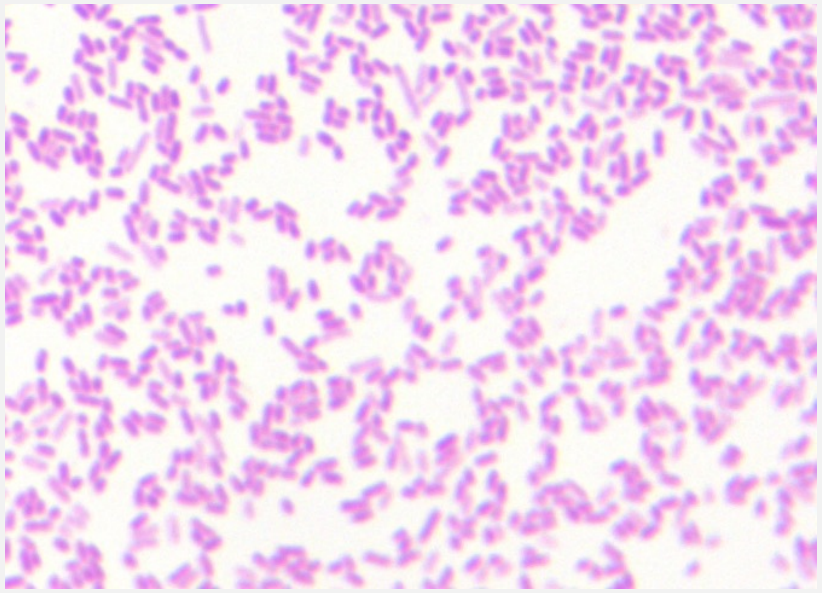
Salmonella Poona has:
O antigens 13 or 22
Phase 1 H antigen z
Phase 2 H 1,6

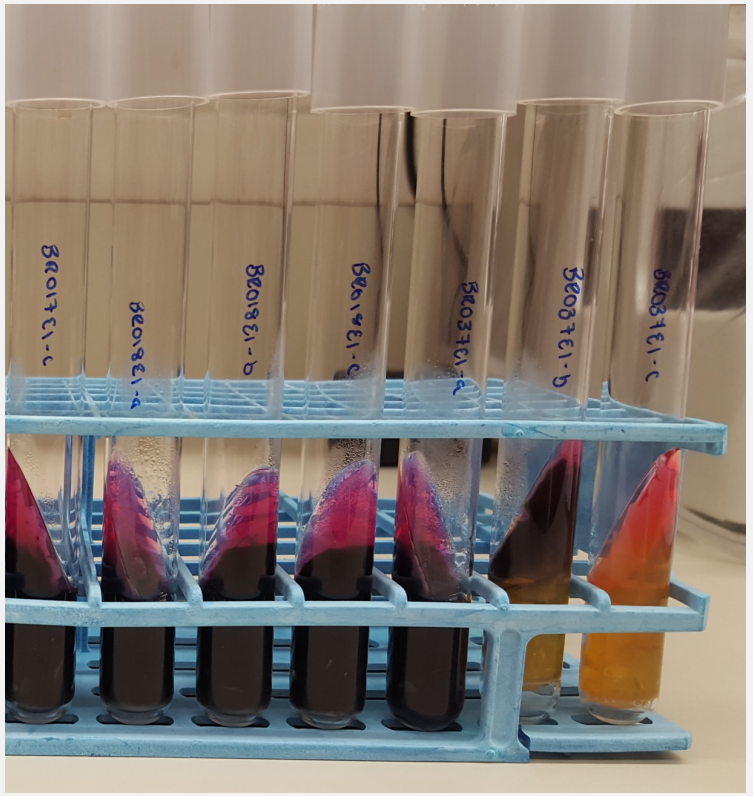
SALMONELLA VIRULENCE FACTORS

- *Salmonella* Pathogenicity Islands (SPI)
  - Gene clusters containing virulence genes
- Type 3 Secretion systems
  - Detects host cells
  - Acts as a needle/syringe to inject effector molecular
  - Involved with invasion
- Fimbriae
  - Adherence and colonization

LABORATORY IDENTIFICATION

- *Salmonella* spp.
  - Culture – selective media





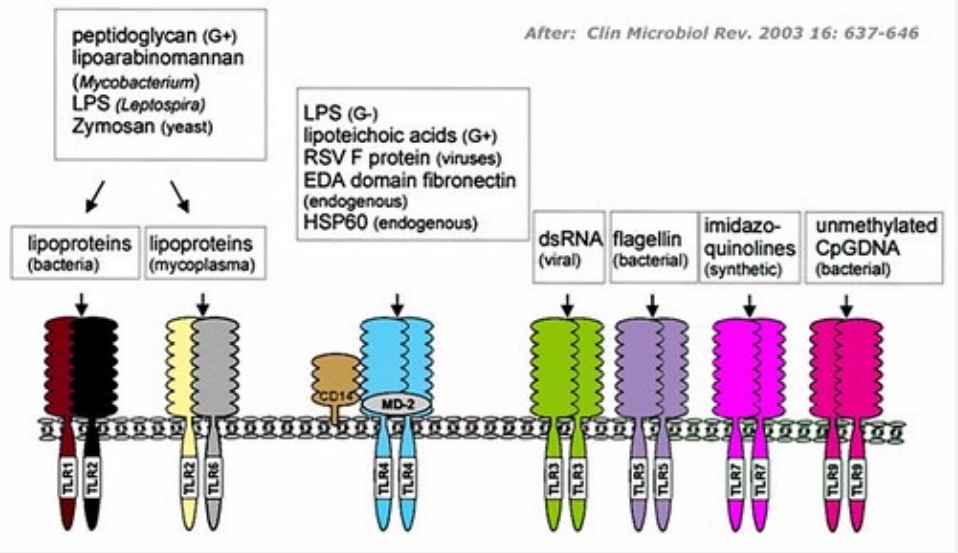
CHRONIC DIARRHEA

IBD AKA CHRONIC ENTEROPATHY

- 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
  - Systematically eliminate the potential 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



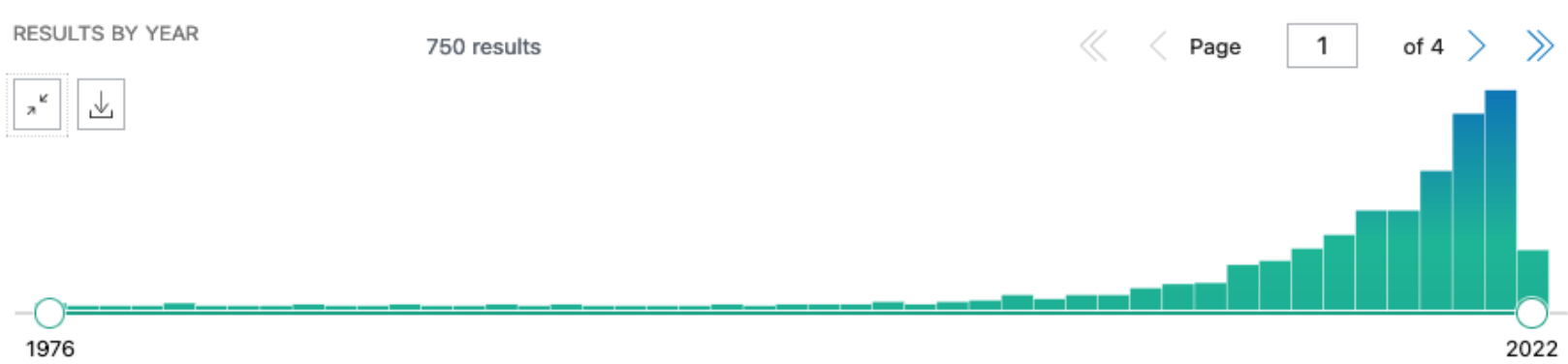
INTESTINAL MUCOSAL IMMUNE SYSTEM

- 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

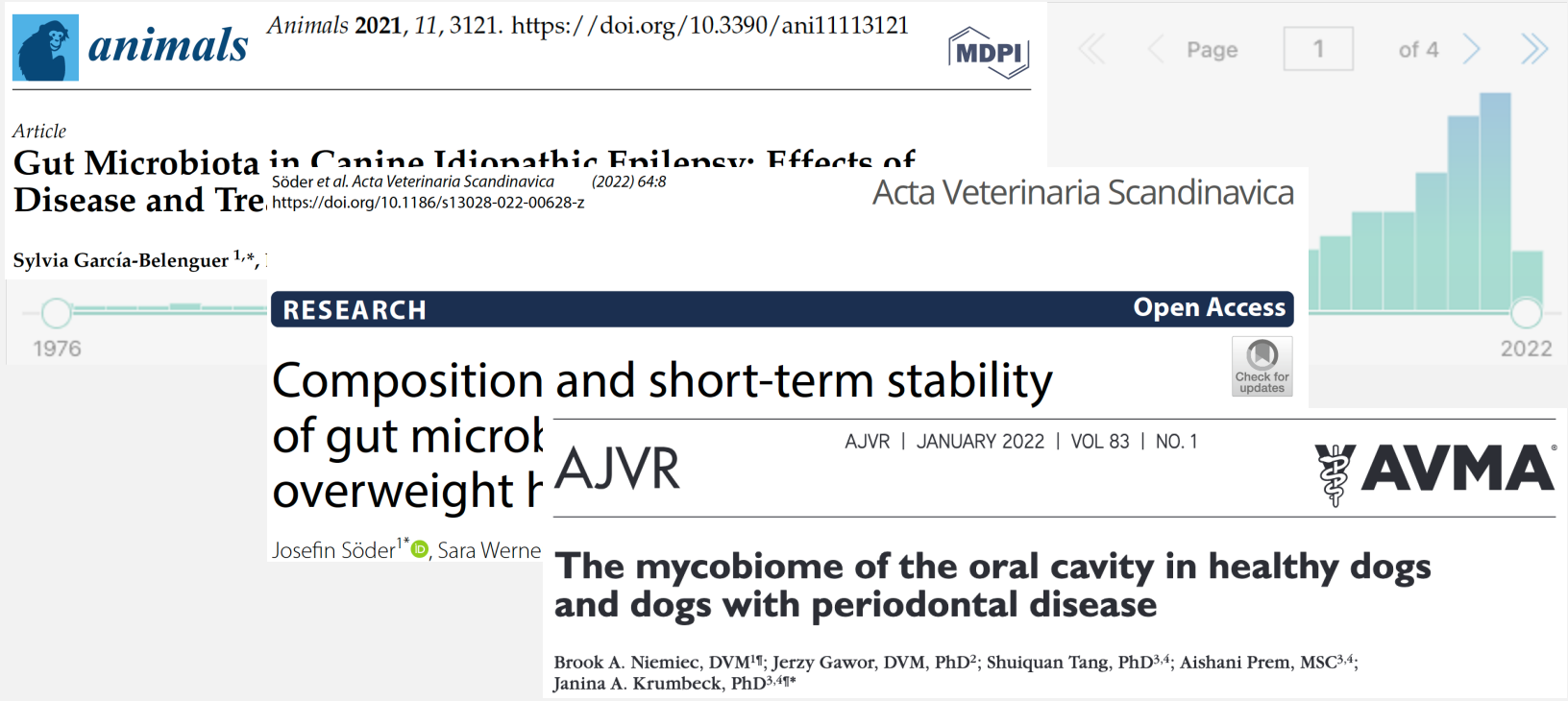
INTESTINAL MICROBIOTA

- 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)
  - What we used to call SIBO
- Will likely be a rapidly changing area for us in the future

A GROWING MICROBIOME LITERATURE



A GROWING MICROBIOME LITERATURE



animals

Animals 2021, 11, 3121. https://doi.org/10.3390/ani11113121

MDPI

Article

Gut Microbiota in Canine Idiopathic Epilepsy: Effects of Disease and Tre

Sylvia García-Belenguer [1,*],

Page 1 of 4

1976

2022

Söder et al. Acta Veterinaria Scandinavica (2022) 64:8
https://doi.org/10.1186/s13028-022-00628-z

Acta Veterinaria Scandinavica

RESEARCH

Open Access

Composition and short-term stability of gut microb overweight h

Check for updates

Josefin Söder[1*], Sara Werne

AJVR

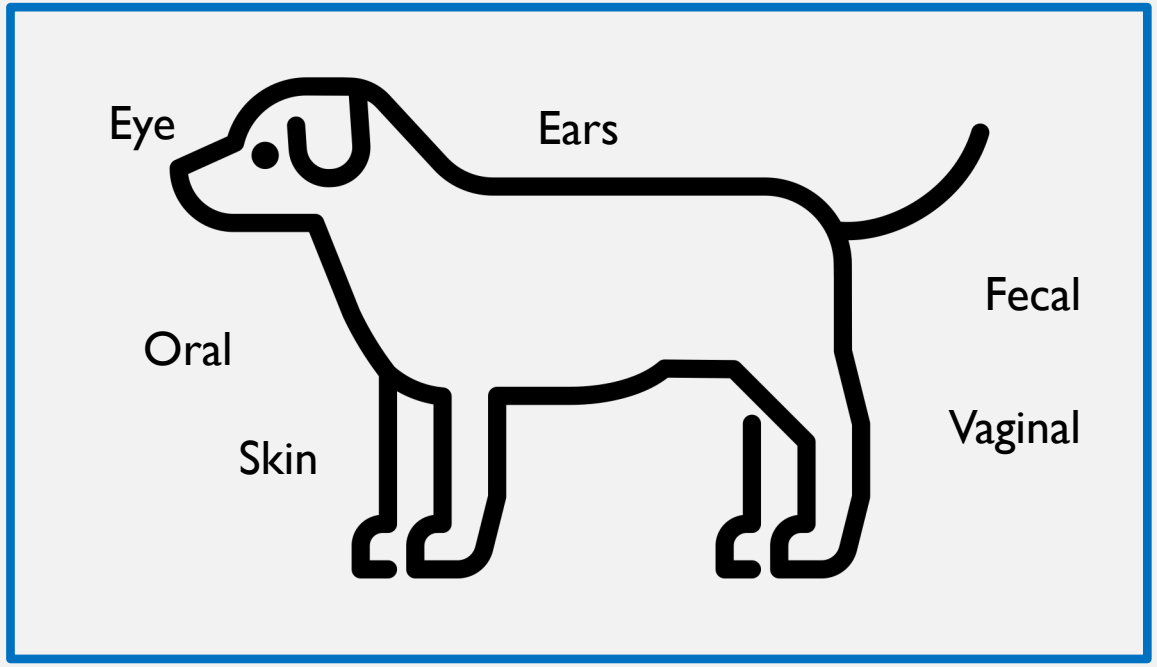
AJVR | JANUARY 2022 | VOL 83 | NO. 1

AVMA

The mycobiome of the oral cavity in healthy dogs and dogs with periodontal disease

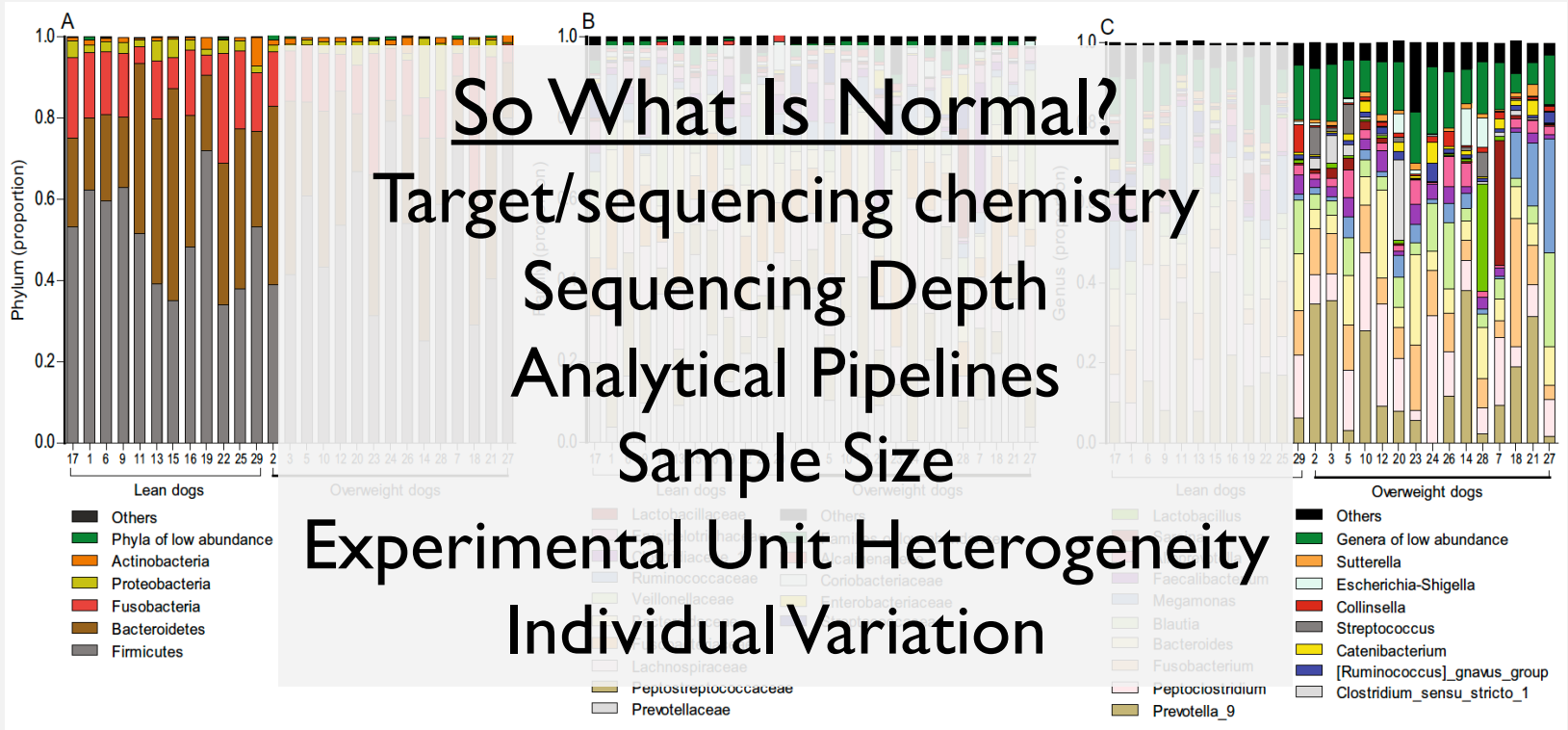
Brook A. Niemiec, DVM[1¶]; Jerzy Gawor, DVM, PhD[2]; Shuiquan Tang, PhD[3,4]; Aishani Prem, MSC[3,4]; Janina A. Krumbeck, PhD[3,4¶*]

WHAT IS A MICROBIOME?



A defined microbial community; could be a particular anatomical site, or the entire host.

HOW DO WE DESCRIBE A MICROBIOME?



So What Is Normal?

Target/sequencing chemistry

Sequencing Depth

Analytical Pipelines

Sample Size

Experimental Unit Heterogeneity

Individual Variation

Söder et al. Acta Veterinaria Scandinavica (2022) 64:8
https://doi.org/10.1186/s13028-022-00628-z

Acta Veterinaria Scandinavica

RESEARCH Open Access

Composition and short-term stability of gut microbiota in lean and spontaneously overweight healthy Labrador retriever dogs

Josefin Söder[1*], Sara Wernersson[2], Katja Höglund[2], Ragnvi Hagman[1], Sanna Lindåse[1] and Johan Dicksved[3]

ACVIM Consensus Statement

J Vet Intern Med 2011;25:1195–1208

Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the Journal of Veterinary Internal Medicine, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

Enteropathogenic Bacteria in Dogs and Cats: Diagnosis, Epidemiology, Treatment, and Control

S.L. Marks, S.C. Rankin, B.A. Byrne, and J.S. Weese

IDENTIFICATION OF INTESTINAL PATHOGENS - PANEL TESTS

- Study included 2 groups of puppies (<1-year-old)
  - Dogs with acute diarrhea, community clinics
  - Matched samples from healthy puppies wo/ diarrhea in past 3 weeks

Veterinary Microbiology 195 (2016) 115–122

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Enteropathogen infections in canine puppies: (Co-)occurrence, clinical relevance and risk factors

Mirjam Duijvestijn[a,*], Lapo Mughini-Gras[a,b], Nancy Schuurman[a], Wim Schijf[a], Jaap A. Wagenaar[a,c], Herman Egberink[a]

IDENTIFICATION OF INTESTINAL PATHOGENS - PANEL TESTS

Table 2
Prevalence of pathogens in diarrhoeic and asymptomatic puppies.

Pathogen	Prevalence in asymptomatic puppies	Prevalence in diarrhoeic puppies	P-value
Salmonella	0% (0/56)	0.9% (1/112)	0.481
Campylobacter	37.5% (21/56)	41.1% (46/112)	0.656
C. perfringens	10.7% (6/56)	18.8% (21/112)	0.183
C. difficile	17.0% (8/47)	15.4% (16/104)	0.799
hEC	1.8% (1/56)	7.4% (8/108)	0.117
Toxocara	5.7% (3/53)	4.6% (5/109)	0.829
Cystoisospora	10.7% (6/56)	18.3% (20/109)	0.205
Giardia	7.1% (4/56)	9.2% (10/109)	0.660
Cyniclomyces	7.1% (4/56)	11.0% (12/109)	0.430
CPV	10.2% (5/49)	23.6% (26/110)	**0.027**
CCoV	14.8% (8/54)	40.2% (43/107)	**0.001**

The bold values denote statistically significant p values ($P < 0.05$).

Table 3
Association of pathogens with severity of disease using weighed clinical score system.

Pathogen	Clinical signs score categories				
	Cat 1: mild	*Cat 2: moderate*	*Cat 3: severe*	n	P-value
Campylobacter	43.9% (18/41)	40.0% (16/40)	38.1% (8/21)	102	0.900
C. perfringens	26.8% (11/41)	10.0% (4/40)	19.0% (4/21)	102	0.149
C. difficile	15.8% (6/38)	13.2% (5/38)	26.3% (5/19)	95	0.516
hEC	2.5% (1/40)[a]	2.6% (1/39)[a]	20.0% (4/20)[b]	99	**0.021**
Toxocara	2.4% (1/41)	2.6% (1/39)	5.3% (1/19)	99	0.796
Cystoisospora	22.0% (9/41)	10.3% (4/39)	26.3% (5/19)	99	0.225
Giardia	17.1% (7/41)	5.1% (2/39)	0.0% (0/19)	99	0.079
Cyniclomyces	14.6% (6/41)	10.3% (4/39)	5.3% (1/19)	99	0.708
CPV	14.6% (6/41)[a]	13.2% (5/38)[a]	61.9%(13/21)[b]	100	**0.000**
CCoV	22.5% (9/40)[a]	39.5% (15/38)[ab]	57.1% (12/21)[b]	99	**0.025**

P-value = overall p-value for the differences among the groups (chi-square test).
[a,b]Each superscript letter denotes a subset of clinical score categories in whose column proportions do not differ significantly from each other at the 0.05 level.
The bold values denote statistically significant p values ($P < 0.05$).

TEST	RESULT
Toxoplasma gondii RealPCR	Negative
Tritrichomonas foetus/blagburni RealPCR	Negative
Cryptosporidium spp. RealPCR	Negative
Giardia spp. RealPCR	Negative
Salmonella spp. RealPCR	Negative
Feline Coronavirus RealPCR	Negative
Feline Panleukopenia Virus RealPCR	Negative
Campylobacter jejuni RealPCR	Negative
Campylobacter coli RealPCR	Negative
C. perfringens Alpha Toxin (CPA) Gene Quant RealPCR	Negative
C. perfringens Enterotoxin (CPE) Gene Quant RealPCR	Negative

DIARRHEA PCR

TEST		RESULT
Diarrhea RealPCR Panel Comment:	a	*

a A POSITIVE FELINE DIARRHEA PANEL PCR result indicates that the nucleic acid (DNA or RNA) of that organism was detected in the fecal sample. This supports infection with this organism(s). Vaccination with a modified live coronavirus vaccine may result in positive results for these viruses for up to a few weeks post-vaccination. Clostridium perfringens toxin genes (CPA, CPE) positive PCR results should be interpreted based on their quantitative levels.

A NEGATIVE FELINE DIARRHEA PANEL PCR result indicates that the nucleic acid (DNA or RNA) of that organism(s) was not detected in this sample and suggests the diarrhea is not caused by this organism(s). However, a negative PCR result may be caused by the numbers of organisms being below the limit of detection, decreased numbers of organisms following treatment or chronic carrier state, or the occurrence of new strain.

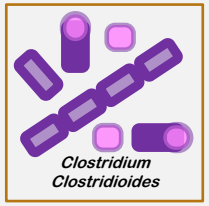
INTERPRETING MULTIPLEX ASSAYS

Diagnostic yield of fecal is low (10.8%), of 260 dogs with diarrhea these tests led to diagnosis.

False positives important because causality not established - issue with PCR?

How does the test change what you do?

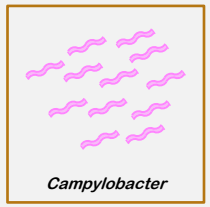
INFECTIOUS DIARRHEA?



Clostridioides difficile → Role in disease unclear, causal association has not been demonstrated.

Clostridium perfringens → Role in disease unclear, enterotoxin found in 80% of healthy and diarrheic dogs. Spore counts inconclusive… no gold standard to diagnose

Salmonella → Prevalence similar in healthy and diarrheic animals. Role possible in acute infection, no evidence for antimicrobials unless systemic disease.



Campylobacter → Prevalence similar in healthy and diarrheic animals. Mild disease in experimental infections. Puppies more likely to be severely affected, experimentally infected kittens didn't show signs.

INFECTIOUS DIARRHEA?

Escherichia coli		Role in granulomatous colitis in Boxer dogs. Generally isolated from dogs and cats with and without diarrhea
Giardia and *Crypto*		Giardia - high frequency of shedding in healthy animals. Perhaps pathogenic in puppies and kittens <6 months. Crypto - 5% of healthy animals positive. Puppies/kittens, stressed and immunocompromised most likely to be affected.
Canine distemper virus		Young dogs or those with incomplete vaccination history. What other signs are present? Predominantly respiratory and neurological… GI not often primary presentation.
Canine circovirus		Little evidence that it's a primary pathogen, may co-infect with canine parvovirus.

INFECTIOUS DIARRHEA?

Canine enteric corona virus → Role in disease unclear, found in 2-33% of healthy dogs. May play role in polymicrobial infections (with parvo and distemper), most often infections self limited.

Parvo

Canine parvovirus → Unvaccinated dogs under 6 months most commonly affected. Virus shed in feces 3 days post-infection, peaks at 4-7 days then declines.

ACVIM Consensus Statement

J Vet Intern Med 2011;25:1195–1208

Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the Journal of Veterinary Internal Medicine, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

Enteropathogenic Bacteria in Dogs and Cats: Diagnosis, Epidemiology, Treatment, and Control

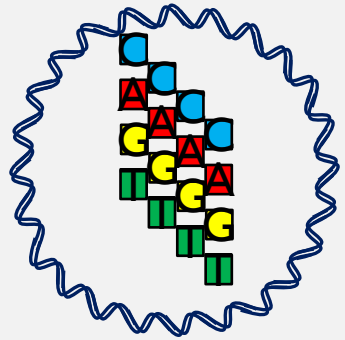
S.L. Marks, S.C. Rankin, B.A. Byrne, and J.S. Weese

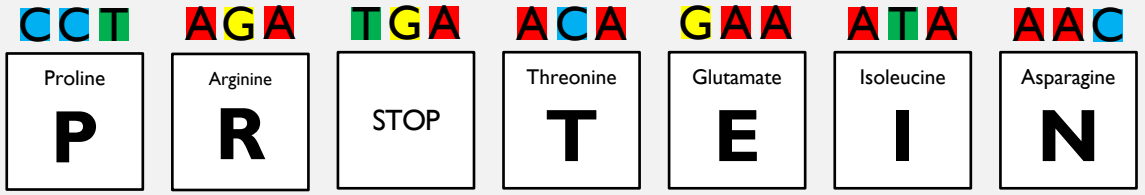
Veterinarians should be cognizant of the fact that most bacterial enteropathogens are associated with self-limiting diarrhea, and the injudicious administration of antimicrobials could be more harmful than beneficial. Supportive therapy and appropriate hygiene control should be considered in all animals with suspected or confirmed bacterial-associated diarrhea (with the exception of *E. coli* associated with granulomatous colitis in which antimicrobial therapy is warranted), and antimicrobials should only be administered to animals manifesting systemic signs of illness.

How will these results positively impact patient management?

MOLECULAR TESTS (DNA)

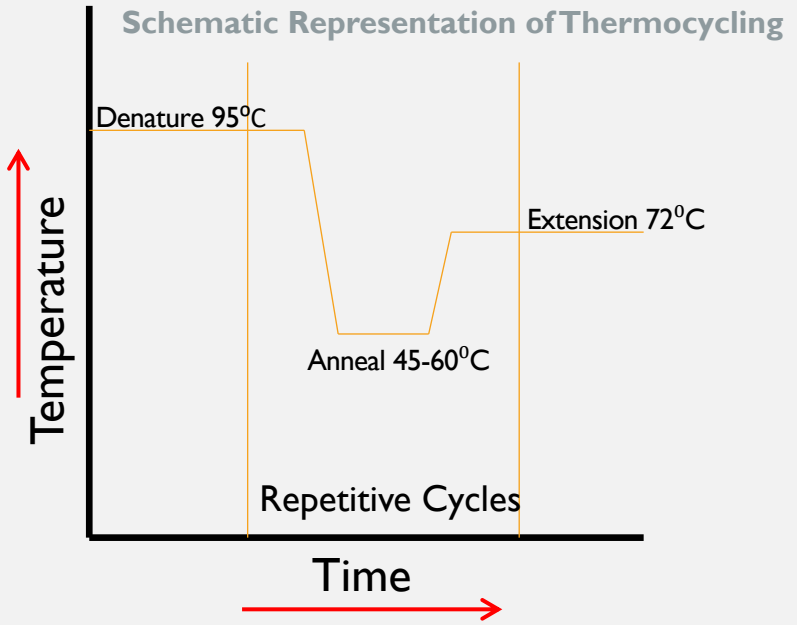
- No amplification (Probe based assays)
- Amplification required (PCR)
- Post-amplification analysis (Amplicon processing or sequencing)
  - Polynucleotides
    - DNA (A, T, G, C); RNA (A, U, G, C)
  - Base pairing
    - A+T (2 bonds); G+C (3 bonds)
  - Sugar + phosphate backbone



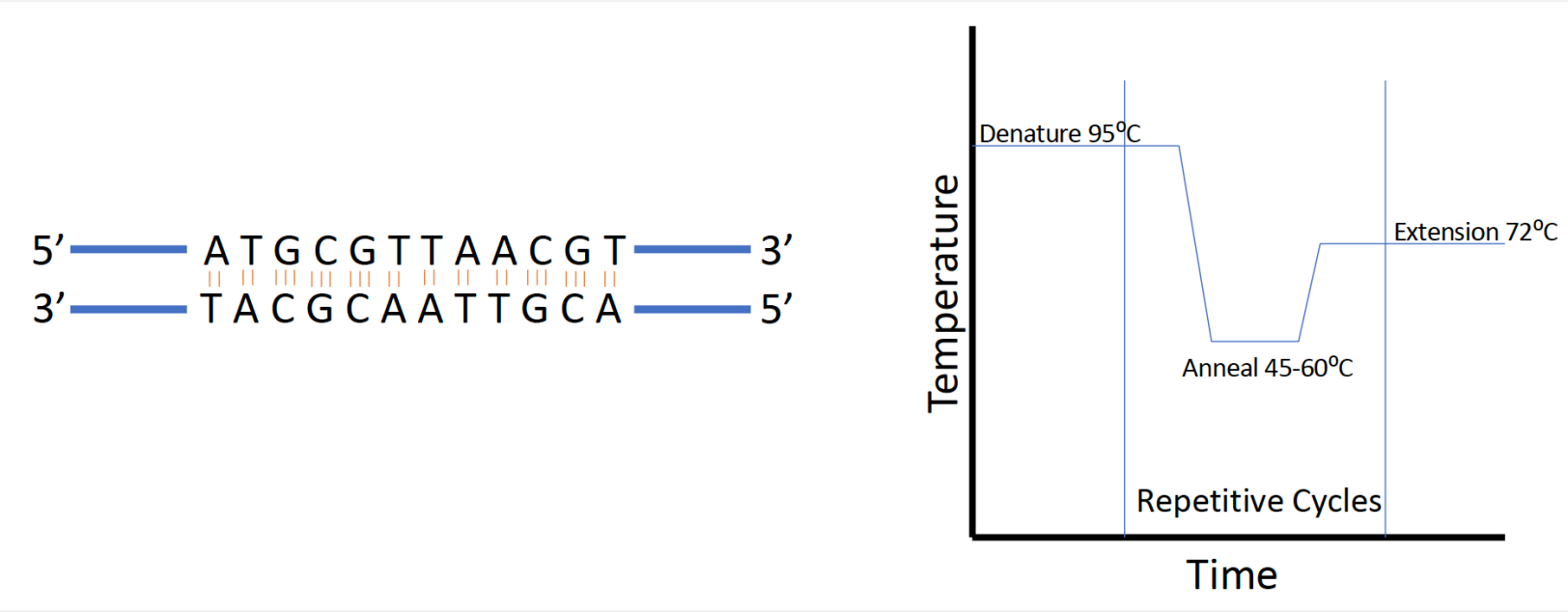


HOW DO WE IDENTIFY DNA SEQUENCES?

- Mimics natural DNA replication processes
- Allows for the amplification of specific DNA sequences
- Polymerase Chain Reaction
  - Specific amplification of DNA
  - Mimics natural DNA replication process
  - Utilizes thermal cycling to melt and anneal DNA



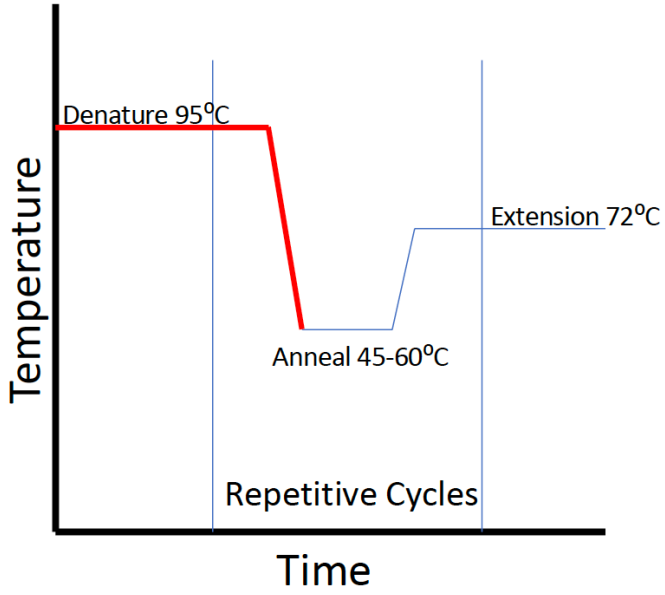
PCR


5’ A T G C G T T A A C G T 3’
3’ T A C G C A A T T G C A 5’
Temperature
Denature 95°C
Anneal 45-60°C
Extension 72°C
Repetitive Cycles
Time

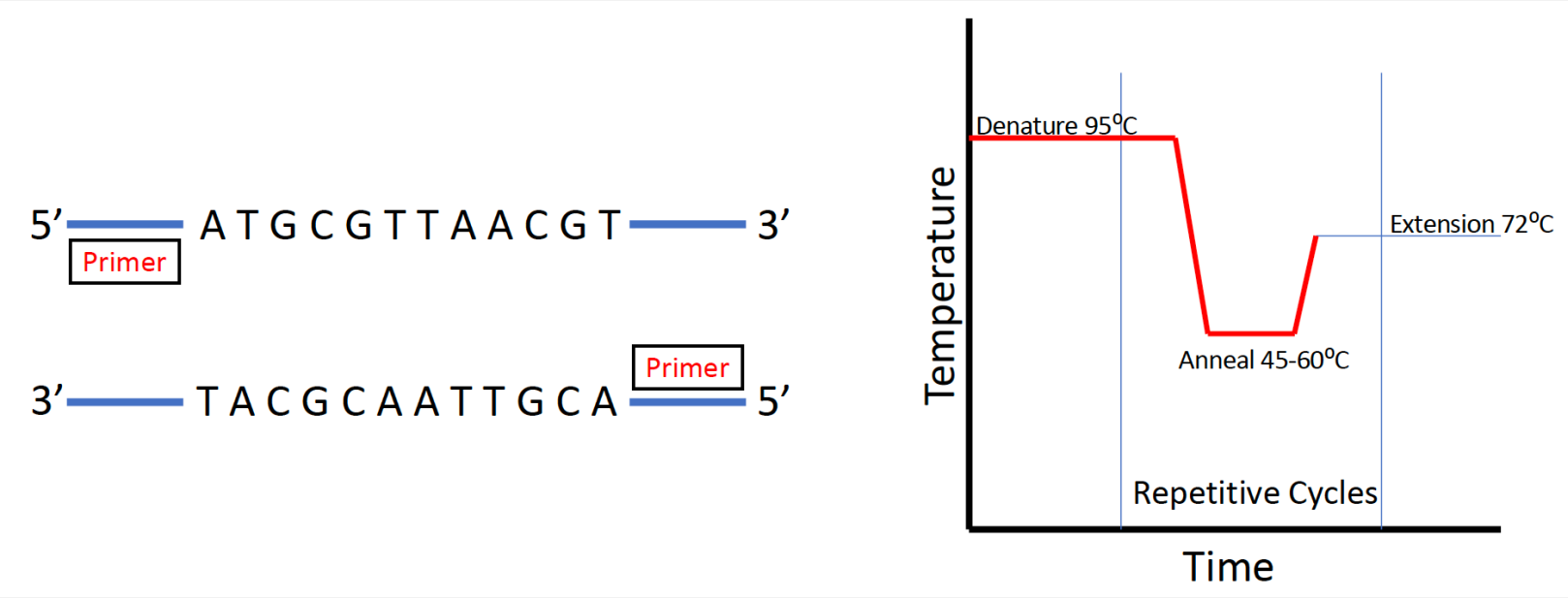
PCR

5’ A T G C G T T A A C G T 3’

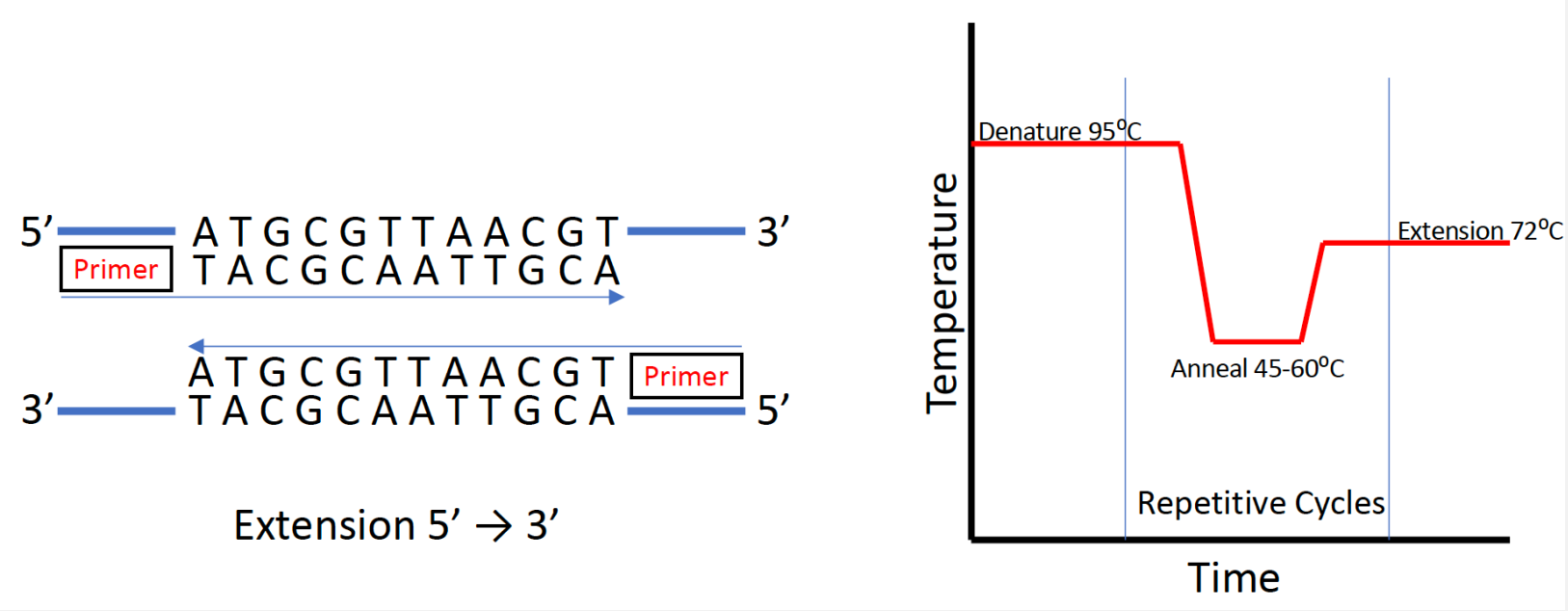
3’ T A C G C A A T T G C A 5’



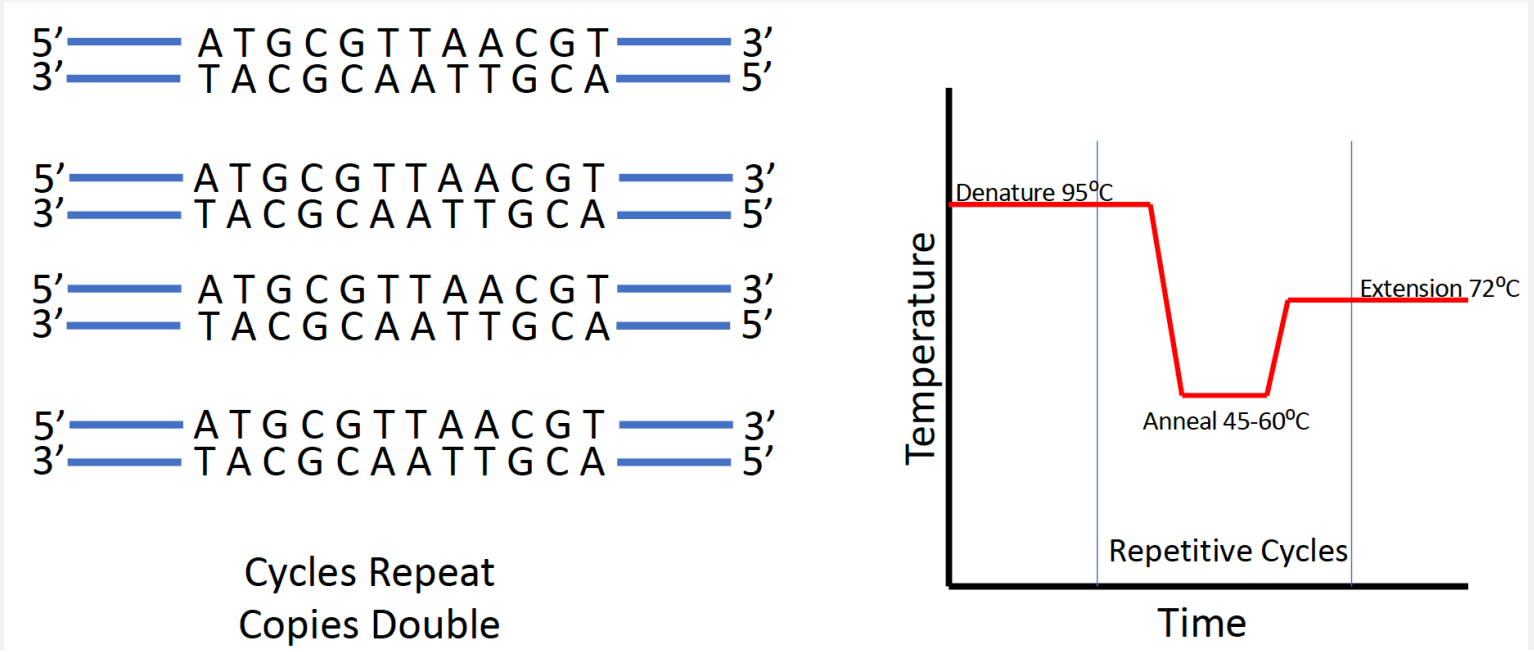
PCR


5’
A T G C G T T A A C G T
3’
Primer
3’
T A C G C A A T T G C A
5’
Primer
Temperature
Denature 95°C
Anneal 45-60°C
Extension 72°C
Repetitive Cycles
Time

PCR

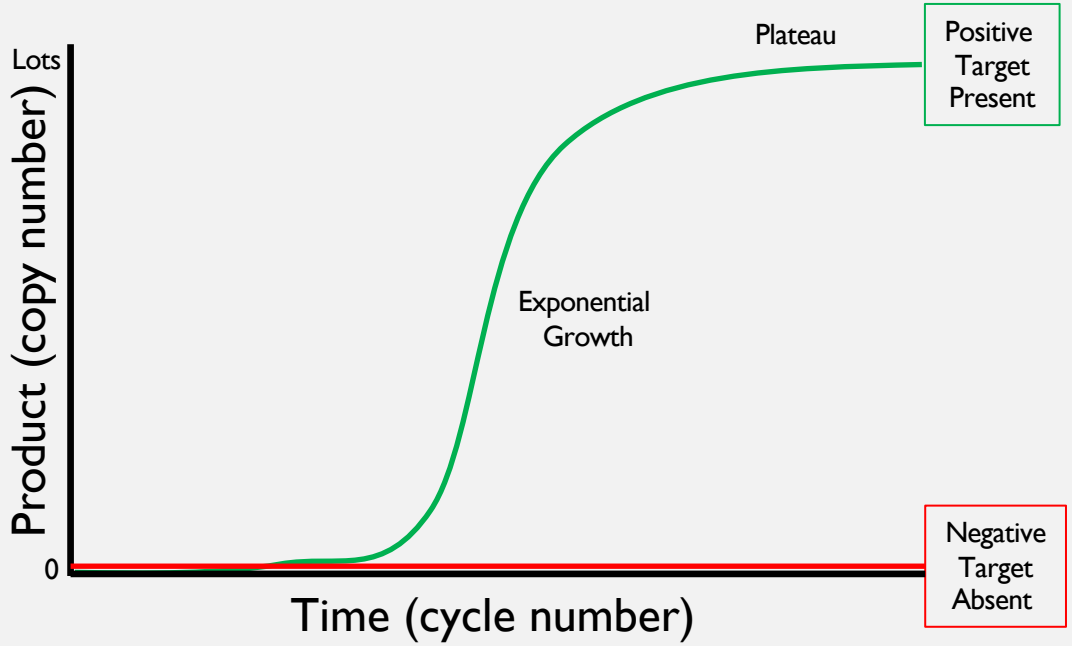

5’
A T G C G T T A A C G T
3’
Primer
T A C G C A A T T G C A
A T G C G T T A A C G T
Primer
3’
T A C G C A A T T G C A
5’
Extension 5’ → 3’
Temperature
Denature 95°C
Extension 72°C
Anneal 45-60°C
Repetitive Cycles
Time

PCR


5’ A T G C G T T A A C G T 3’
3’ T A C G C A A T T G C A 5’
5’ A T G C G T T A A C G T 3’
3’ T A C G C A A T T G C A 5’
5’ A T G C G T T A A C G T 3’
3’ T A C G C A A T T G C A 5’
5’ A T G C G T T A A C G T 3’
3’ T A C G C A A T T G C A 5’
Cycles Repeat
Copies Double
Temperature
Denature 95°C
Anneal 45-60°C
Extension 72°C
Repetitive Cycles
Time


Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9

PCR


Lots
Product (copy number)
0
Time (cycle number)
Plateau
Exponential
Growth
Positive
Target
Present
Negative
Target
Absent

CLASSIFICATIONS OF IBD/CE

- Food responsive enteropathy
- Antibiotic responsive enteropathy
- Immunosuppressive responsive enteropathy
  - True inflammatory disease based on histopathology:
    - Lymphoplasmacytic
    - Eosinophilic
    - Granulomatous
- Special Cases and Breed specific disorders

Enteropathy:

- More inclusive than just saying "diarrhea" or vomiting"
- Helps explain the diffuse and often changing nature of the clinical signs

FOOD RESPONSIVE ENTEROPATHY

The most common cause of chronic diarrhea

Allergies vs intolerance

What does a proper diet trial look like?

Contents
Duration
Response

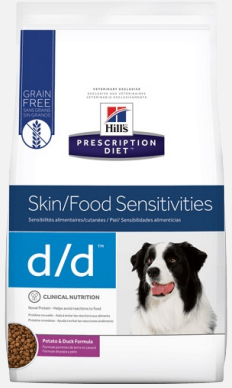
Novels proteins vs hydrolyzed proteins

Homemade diets

Use a nutritionist!!!

DIETARY MANAGEMENT OF IBD/CE

- 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 Wheaton Terriers)
    - Fat malabsorption - i.e. lymphangiectasia
    - Fibre restriction – in patients with excessive bloating/flatulence
      - Low vs medium vs high fermentability of fibre



DIETARY MANAGEMENT

NOVEL PROTEIN SOURCE

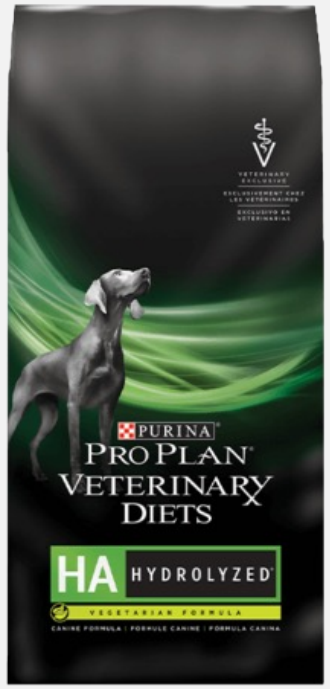
- Protein source that patient has not been exposed to before
  - Can be difficult in some patients
- Theory:
  - Decreases antigenic stimulation of inflammatory response

HYDROLYZED PROTEIN SOURCE

- Small proteins
  - Evade detection by the immune system to reduce inflammatory response
- Easy option
- Price concerns?
- Palatability concerns?

VEGETARIAN FOOD

- HA is a Hydrolyzed protein, soy based
- Royal Canine – soy based protein

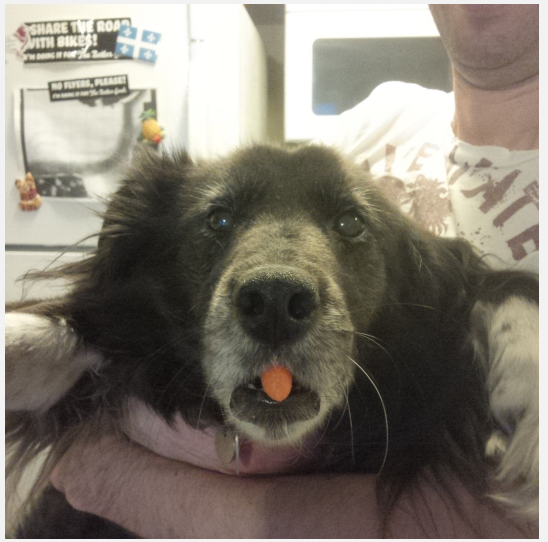


DIET TRIALS

- 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 lease 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, cucumbers
  - 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!

Nutrition Support Service
Veterinary Medical Teaching Hospital
One Shields Ave, Davis, CA 95616-8747
Ph: 530-752-7892 / Fax: 530-752-7901
Email: nssvetmed@ucdavis.edu

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

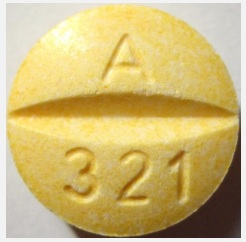
- What does this mean?
  - Acute or chronic diarrhea that responds when treated with antibiotics
    - But not just ANY antibiotic…
- Acute infectious processes
  - *Campylobacter, salmonella,* enteropathogenic e. *coli*
- Dysbiosis/SIBO
- IBD
  - Tylosin-responsive diarrhea
  - Granulomatous colitis

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 (H_2 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 is all you need
  - Tylosin



vetrxdirect.com

WHAT IS TYLOSIN?

- Macrolide antimicrobial
  - Bateriostatic
  - 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

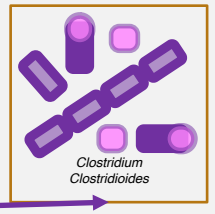
Wedgewood pharmacy: Gourmeds Chewable

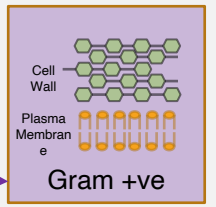
Reversible binding to to 50S ribosomal subunit - bacteriostatic

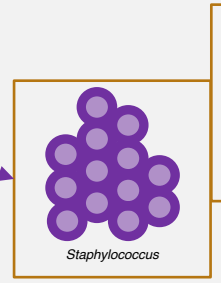
Macrolides

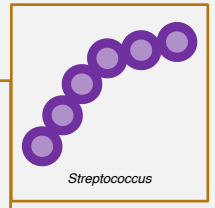
Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin

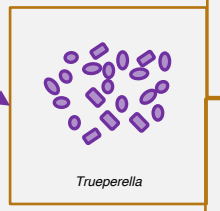
Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

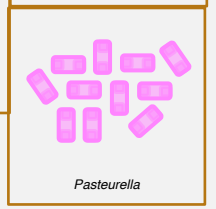


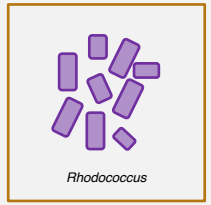


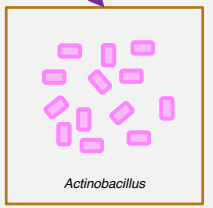


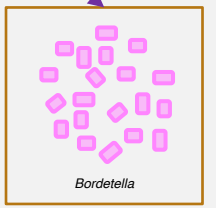












Lincosamides

Clindamycin, lincomycin

Similar to macrolides

Ketolides

Clarithromycin

Similar to macrolides with enhanced Gm pos activity

Azalides

Azithromycin, gamithromycin

Similar to macrolides with enhanced Gram neg activity including Enterobacteriaceae

Streptogramins

Vinginiamycin

Gm pos cocci and bacilli, Gm neg cocci, anaerobes

TYLOSIN RESPONSIVE DIARRHEA

- 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
  - Neutrophilic inflammation

These are NOT super sick dogs!

WHEN TO USE TYLOSIN?

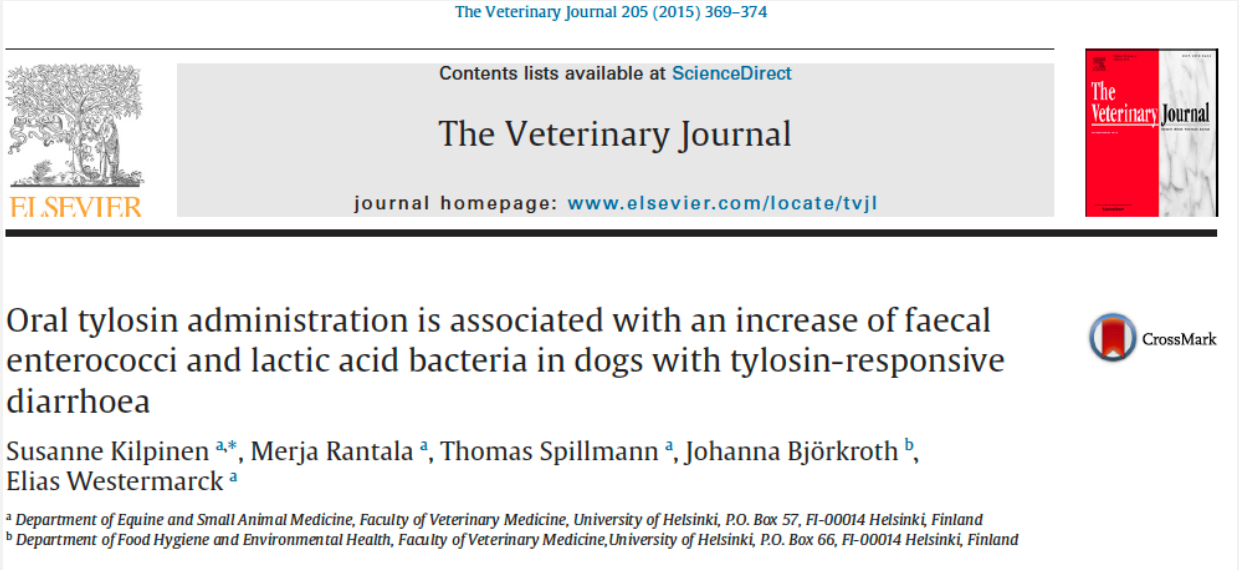
- After we rule out systemic causes of disease
  - CBC, biochemistry, urinalysis
  - Possible TLI
  - Possible infectious disease testing based on patient history
- After a negative fecal and/or appropriate deworming
  - 50mg/kg fenbendazole PO SID x 3 days (repeated in 3 weeks and maybe 3 months)
- 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 3-4 weeks and then reduce treatment to once daily
    - After another 3-4 weeks, try to stop
- 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!)

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:



The Veterinary Journal 205 (2015) 369–374

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

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

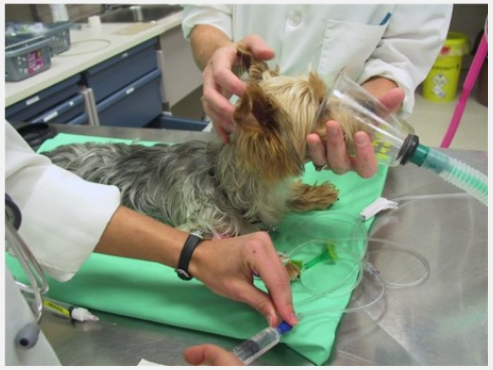
Susanne Kilpinen [a,*], Merja Rantala [a], Thomas Spillmann [a], Johanna Björkroth [b], Elias Westermarck [a]

[a] Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, P.O. Box 57, FI-00014 Helsinki, Finland
[b] Department of Food Hygiene and Environmental Health, Faculty of Veterinary Medicine, University of Helsinki, P.O. Box 66, FI-00014 Helsinki, Finland

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.

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 Wheaton Terriers
  - PLE, gluten intolerance
- Basenji's
  - Rare immunoproliferative enteropathy

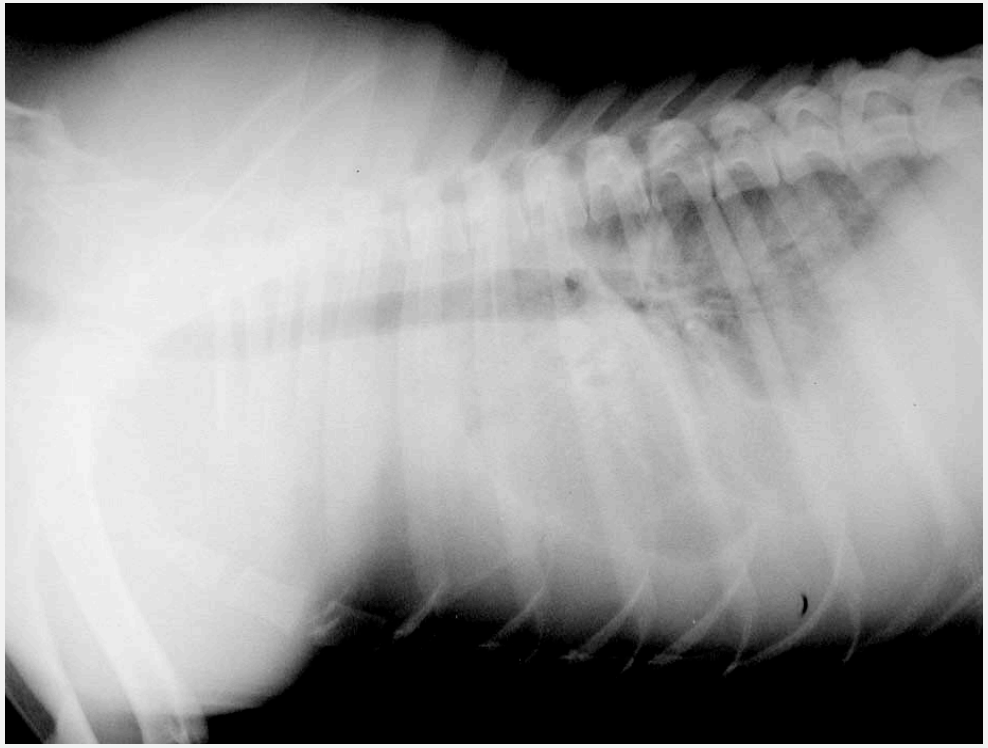


BURTON

- 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
- General History
  - Vaccines "UTD"
  - No travel
  - Other dog in house is healthy
  - Unknown deworming history

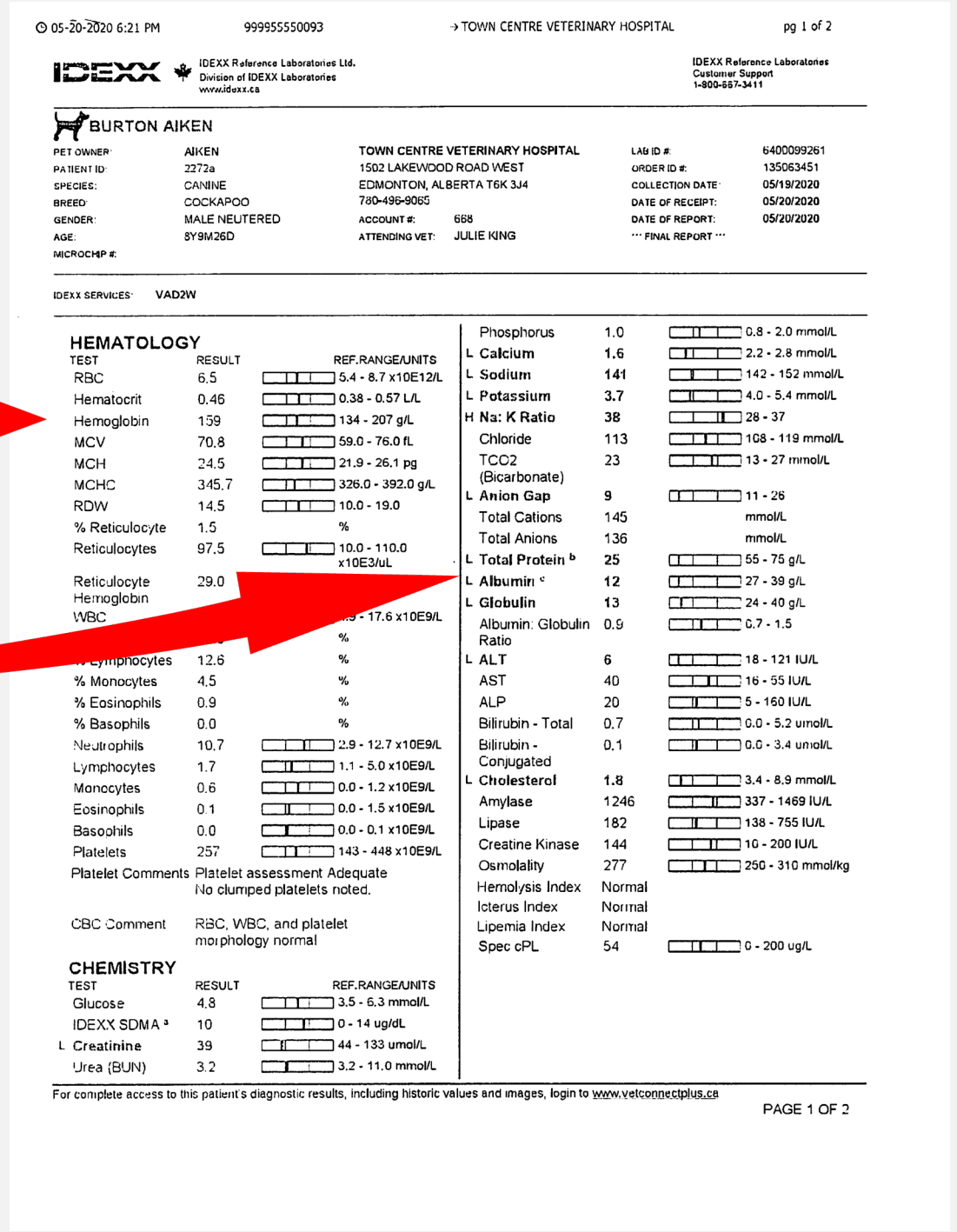
BURTON

- Saw a vet 1 week after the diarrhea began
  - Treated with doxycycline, metronidazole, Metacam
  - No change to diarrhea
- Saw a 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
    - Albumin - 12
    - Globulin - 13
  - Hypocalcemia
  - Hyponatremia
  - Hypokalemia



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Customer Support
1-800-667-3411

BURTON AIKEN

PET OWNER:	AIKEN	TOWN CENTRE VETERINARY HOSPITAL		LAB ID #:	6400099261
PATIENT ID:	2272a	1502 LAKEWOOD ROAD WEST		ORDER ID #:	135063451
SPECIES:	CANINE	EDMONTON, ALBERTA T6K 3J4		COLLECTION DATE:	05/19/2020
BREED:	COCKAPOO	780-496-9065		DATE OF RECEIPT:	05/20/2020
GENDER:	MALE NEUTERED	ACCOUNT #:	668	DATE OF REPORT:	05/20/2020
AGE:	8Y9M26D	ATTENDING VET:	JULIE KING		··· FINAL REPORT ···
MICROCHIP #:					

IDEXX SERVICES: VAD2W

HEMATOLOGY

TEST	RESULT		REF.RANGE/UNITS
RBC	6.5		5.4 - 8.7 x10E12/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 x10E3/uL
Reticulocyte Hemoglobin	29.0		
WBC			17.6 x10E9/L
			%
% Lymphocytes	12.6		%
% Monocytes	4.5		%
% Eosinophils	0.9		%
% Basophils	0.0		%
Neutrophils	10.7		2.9 - 12.7 x10E9/L
Lymphocytes	1.7		1.1 - 5.0 x10E9/L
Monocytes	0.6		0.0 - 1.2 x10E9/L
Eosinophils	0.1		0.0 - 1.5 x10E9/L
Basophils	0.0		0.0 - 0.1 x10E9/L
Platelets	257		143 - 448 x10E9/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

For complete access to this patient's diagnostic results, including historic values and images, login to www.vetconnectplus.ca

PAGE 1 OF 2

STABILIZED THROUGH ER SERVICE

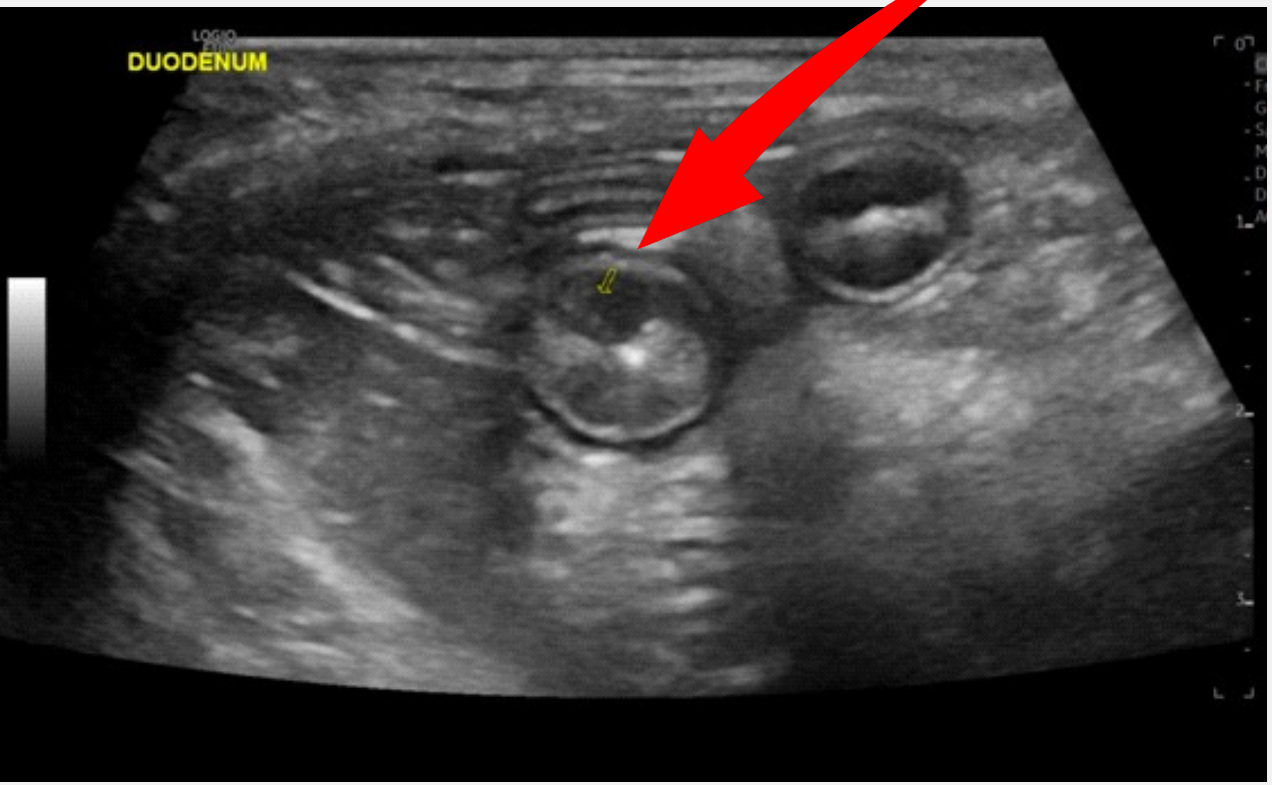
- Thoracocentesis
  - Recovered a pure transudate, fits with the low albumin
- Blood Gas
- Abdominal Ultrasound:
  - **Intestines:** Colon 0.19 cm. Small Intestines 0.36 to 0.42 cm. The small intestinal mucosa is markedly hyperechoic with mucosal striae.
  - Pancreas: Right limb seen, normal size, shape 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.

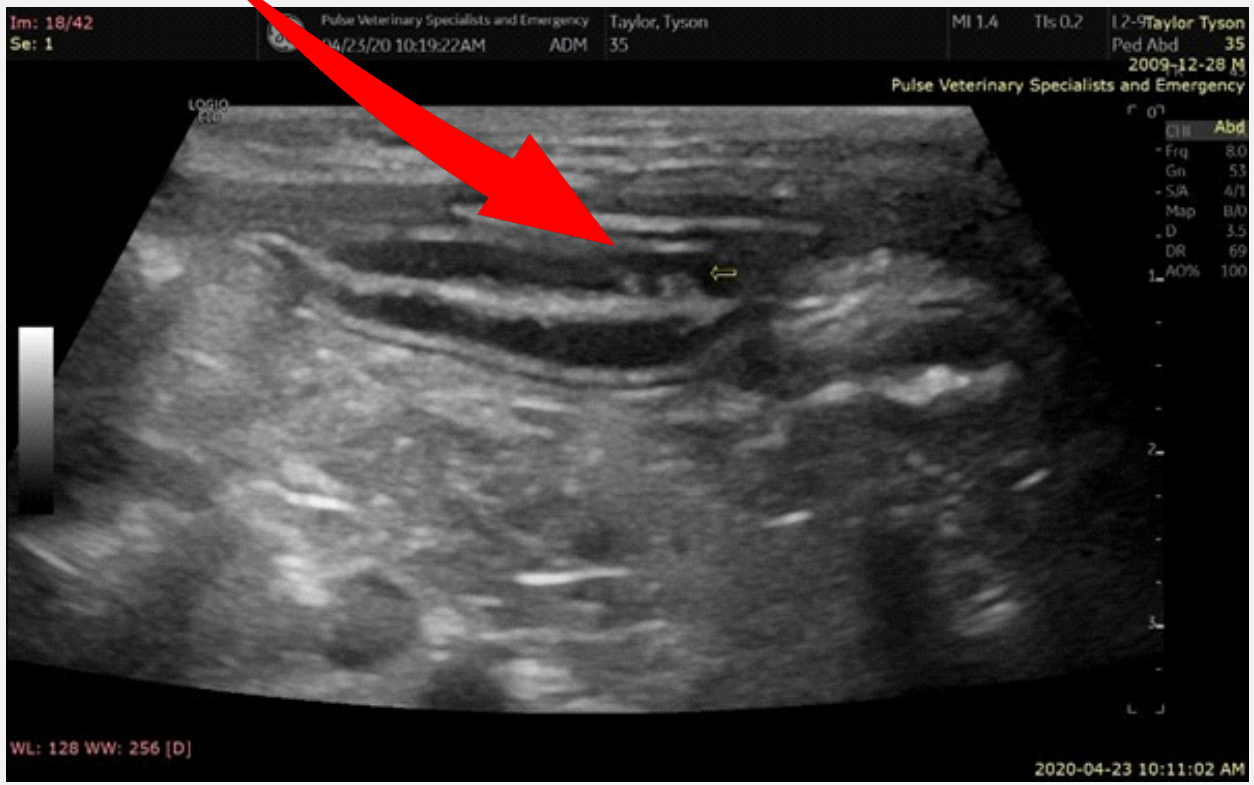
Blood Gas at Admission

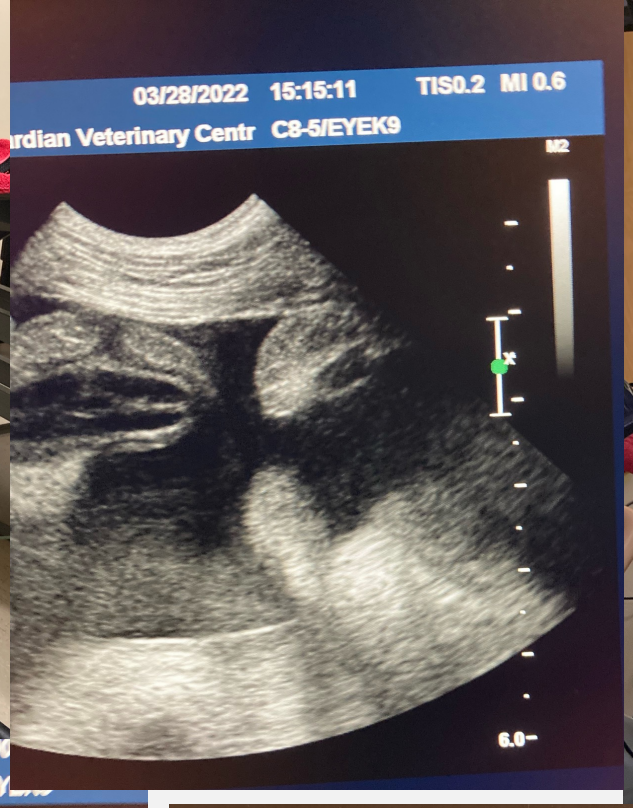
Acid-base status			
pH	7.370		[7.360 - 7.470]
pCO_2	35.6	mmHg	[33.0 - 52.0]
↓ SBE_c	-4.7	mmol/L	[-4.0 - 2.0]
$cHCO_3^-(P)_c$	20.6	mmol/L	
Anion Gap_c	3.3	mmol/L	
↑ cCl^-	121	mmol/L	[106 - 120]
Metabolite values			
↓ cLac	0.5	mmol/L	[0.6 - 2.5]
cGlu	5.0	mmol/L	[4.1 - 6.6]
Electrolyte values			
cNa^+	145	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]

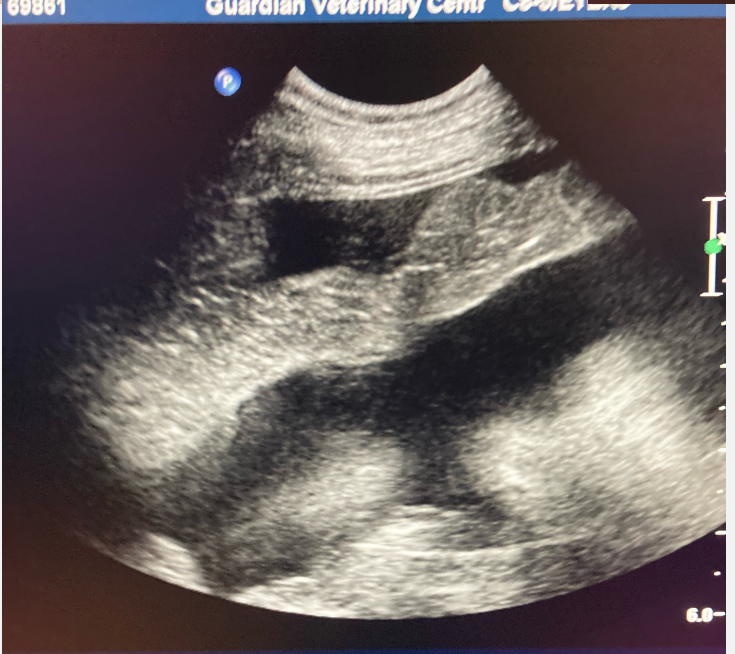
ABDOMINAL ULTRASOUND

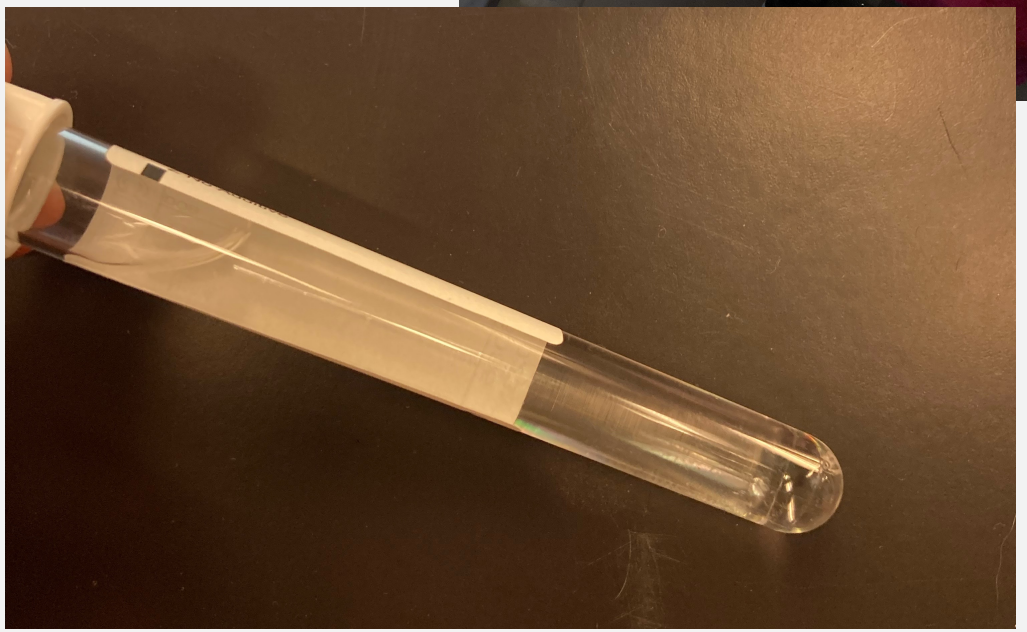
Intestinal wall “striations”











Winston – PLE with acites

Total Protein – 28
Albumin 14
Globulin 14

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 ylosin 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 surgery?

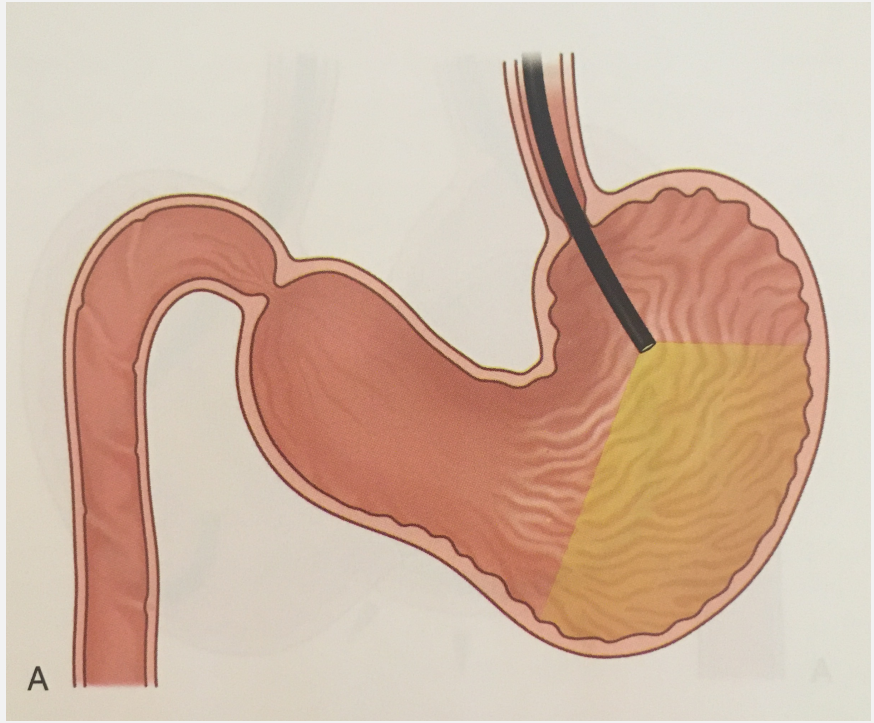
DO WE HAVE TO CONVINCE OWNERS?

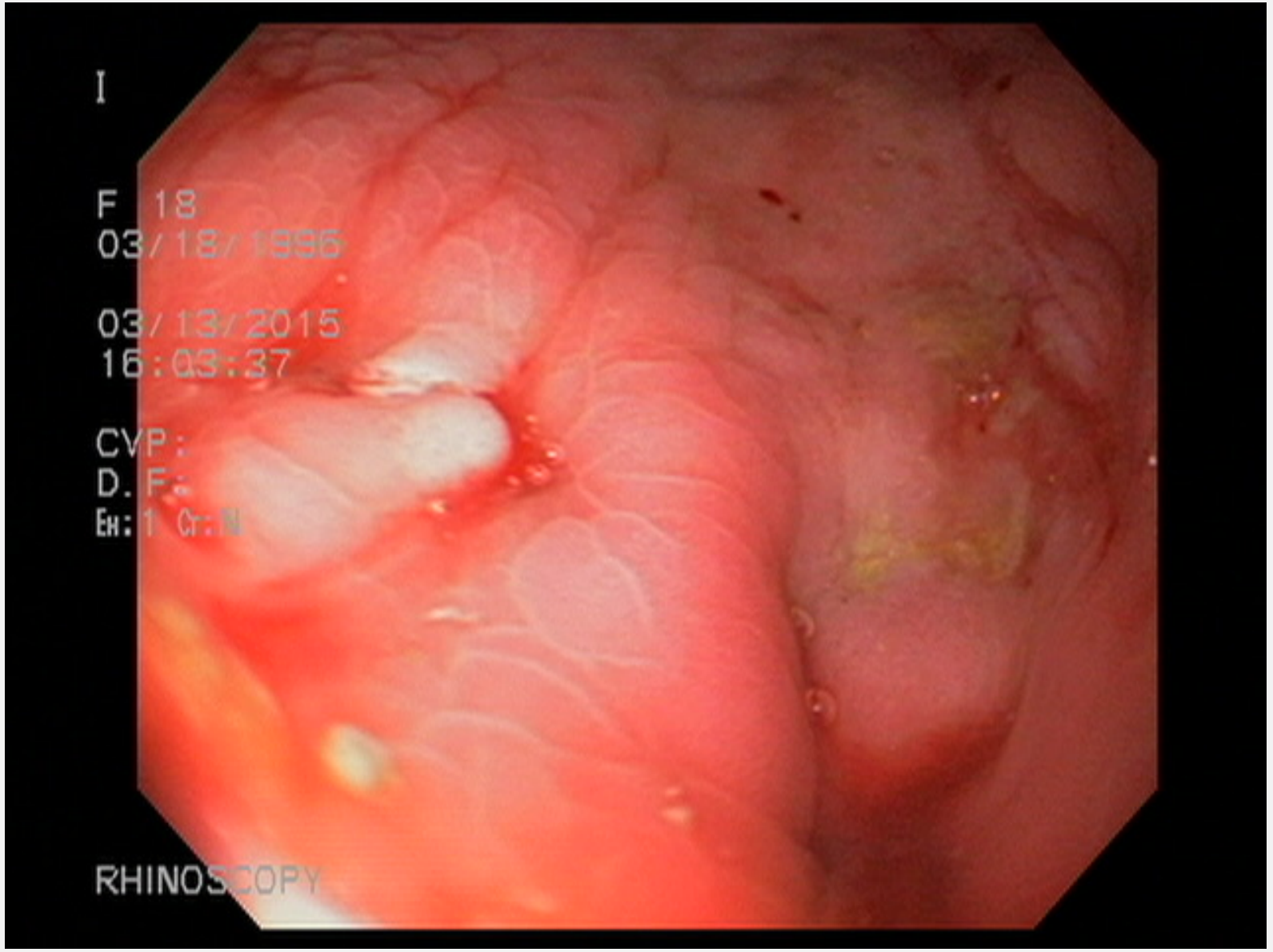
- By the time they come to me, they are usually motivated to go farther
- Why don't I just try meds to see what happens?
  - Is it better because of my drugs?
  - Is it not responding because I have the wrong dose? The wrong drug?
  - Not all cases have significant inflammation, so drugs may not help
    - 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

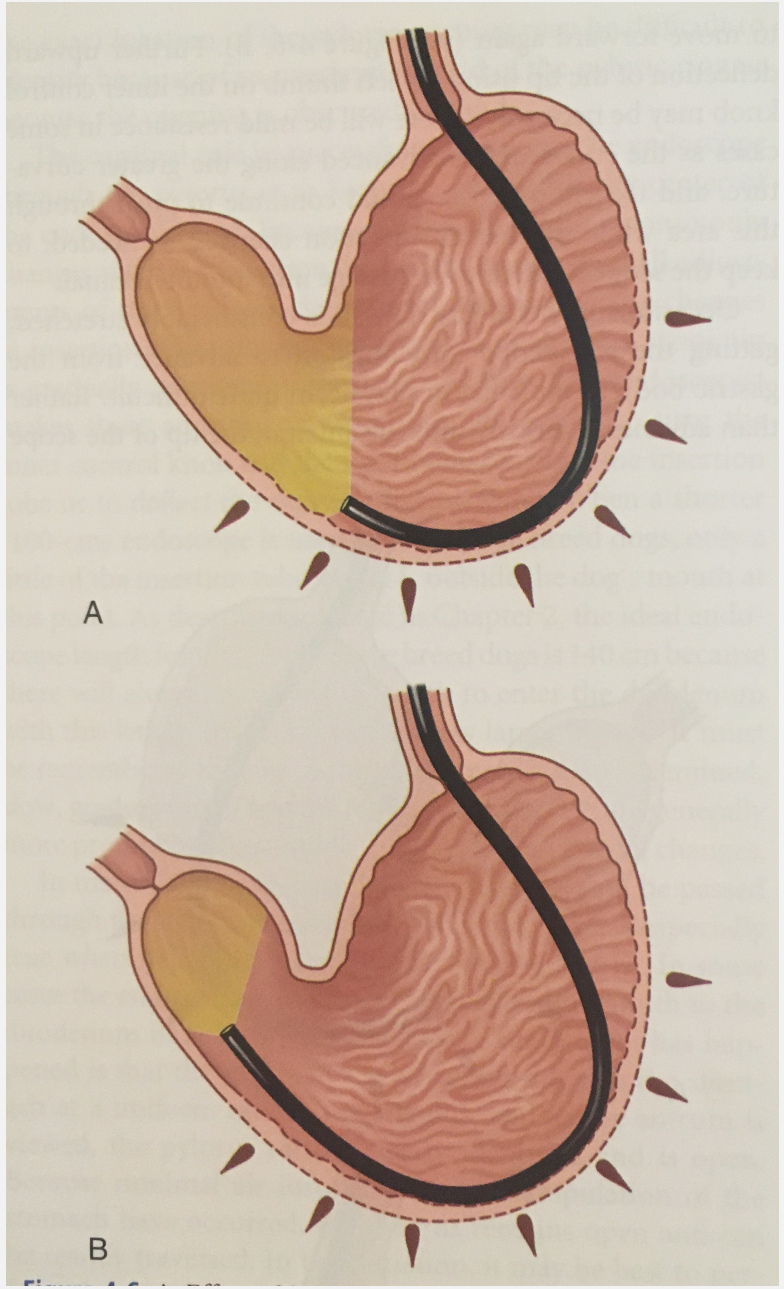
WHAT WOULD ENDOSCOPY HAVE LOOKED LIKE?

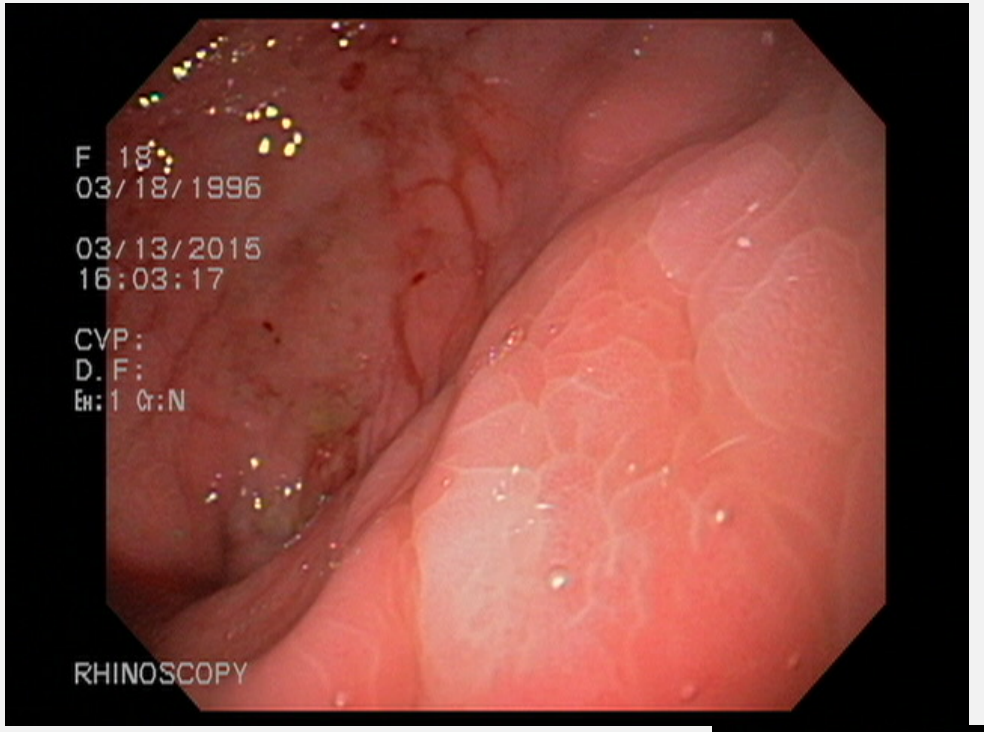
What does endoscopy look like?

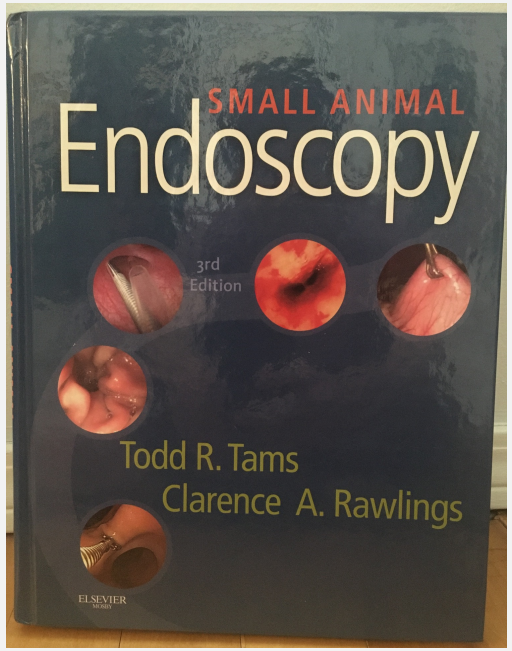
- After we get through the LES
- Looking at Greater Curvature



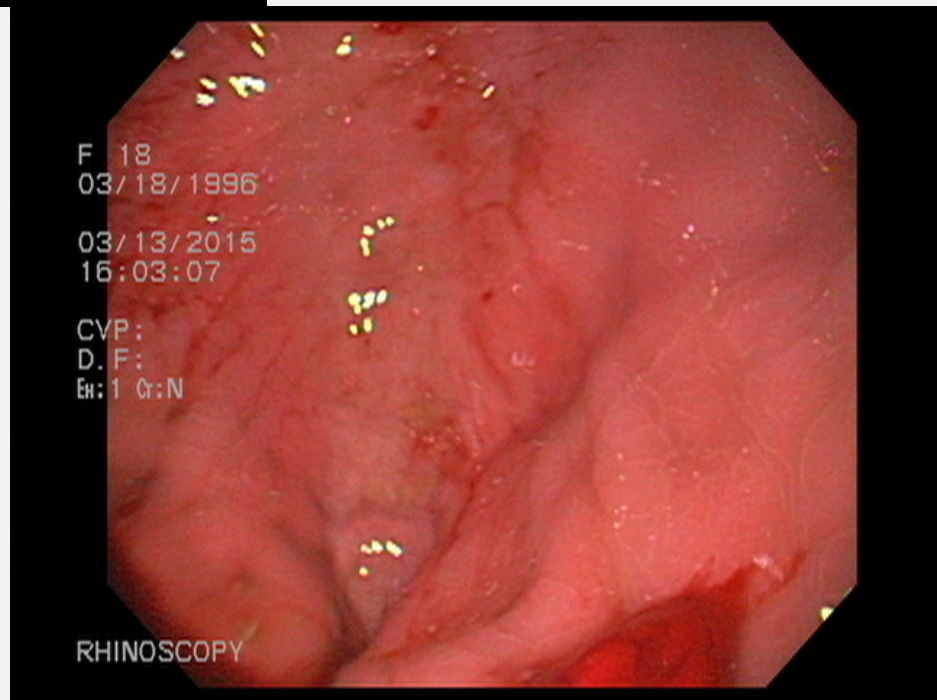


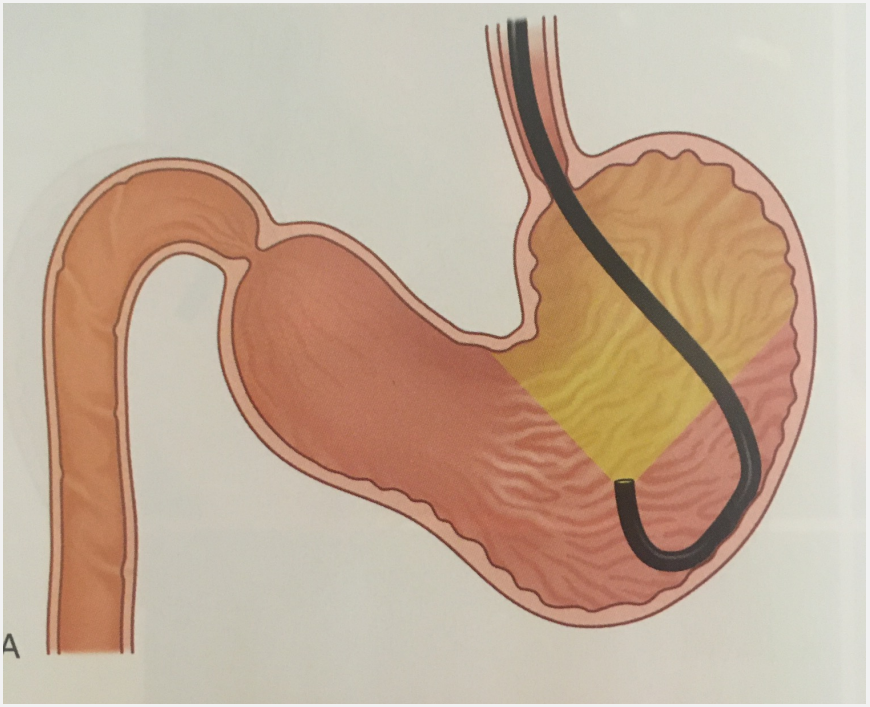






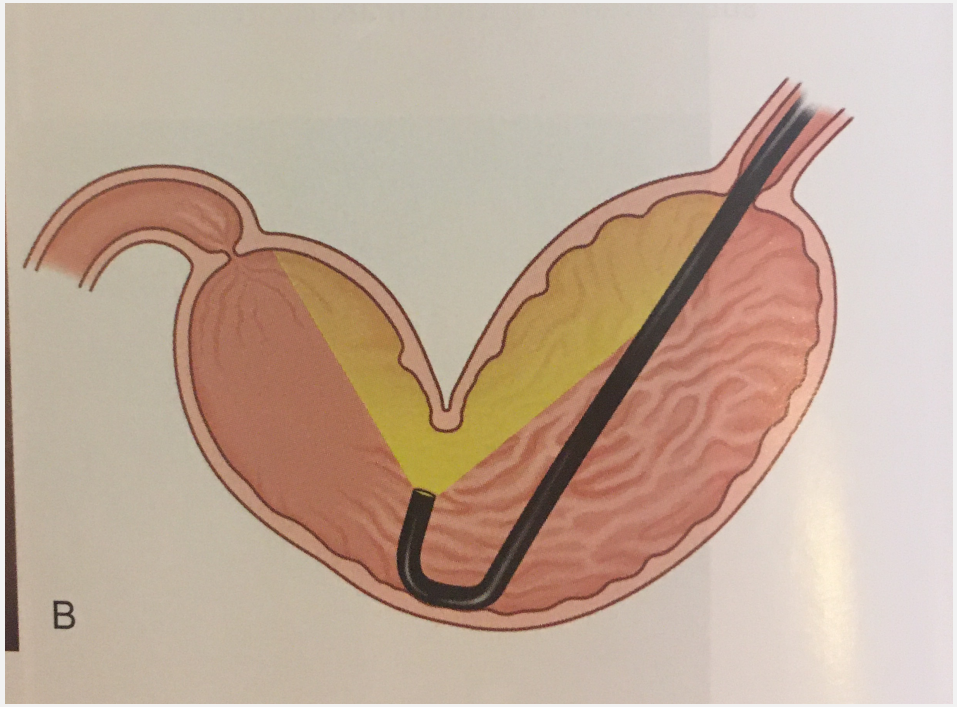
The scope is directed by sliding along the gastric wall, we only control where the tip looks, not where it goes!





This is how we explore the stomach:

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



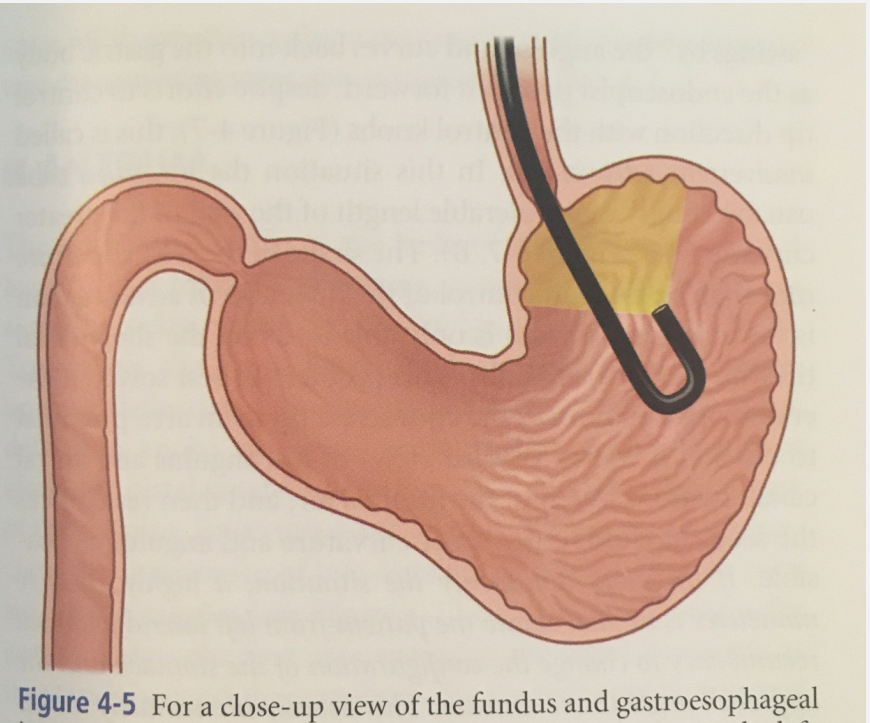
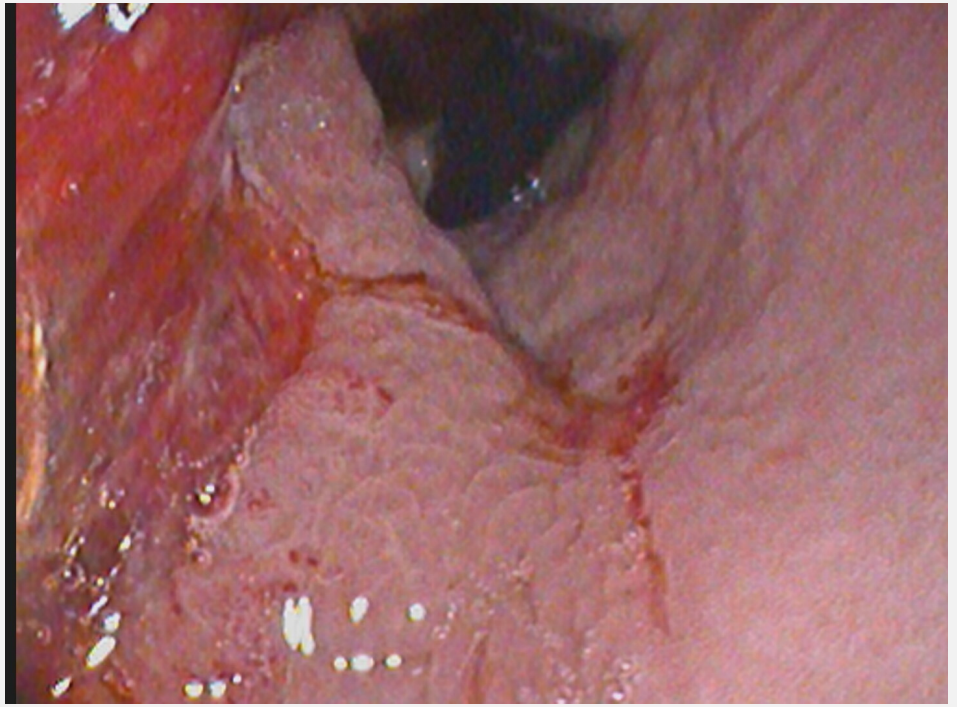


Figure 4-5 For a close-up view of the fundus and gastroesophageal



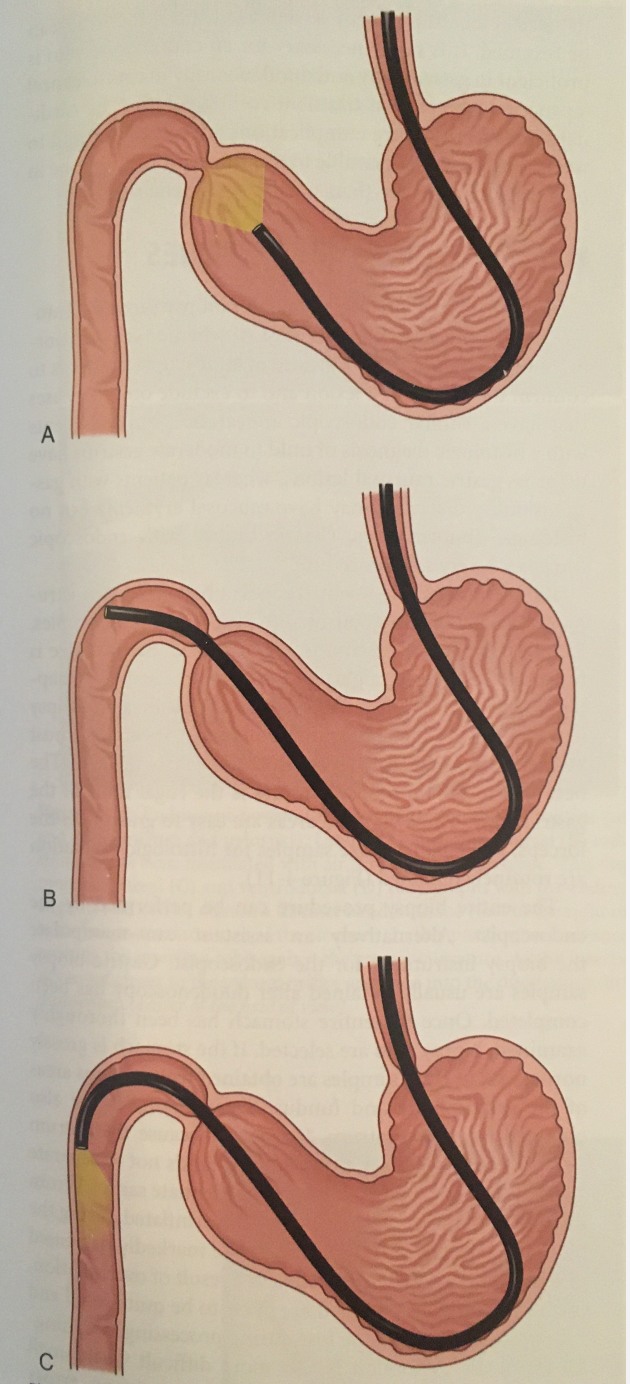
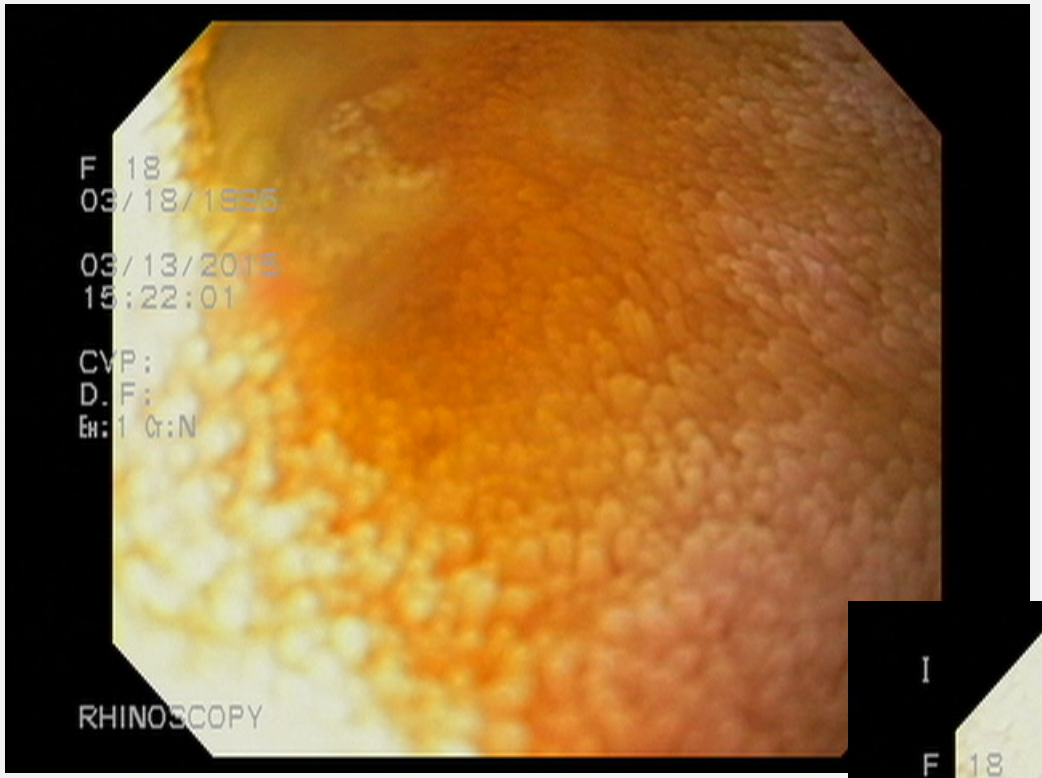
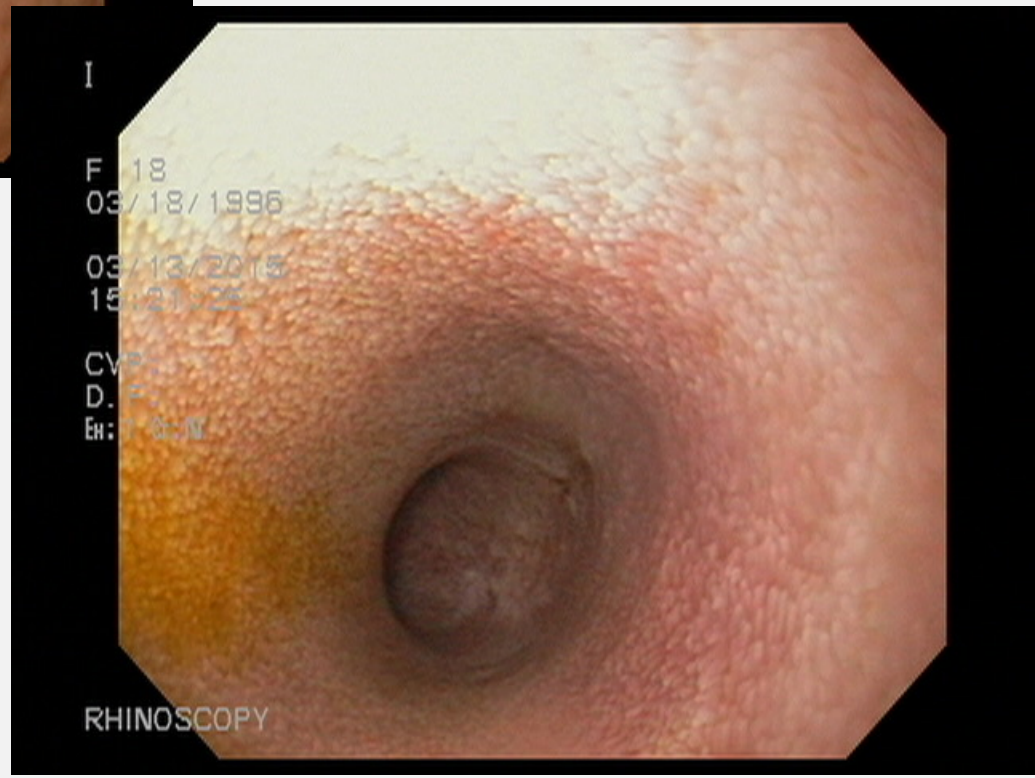
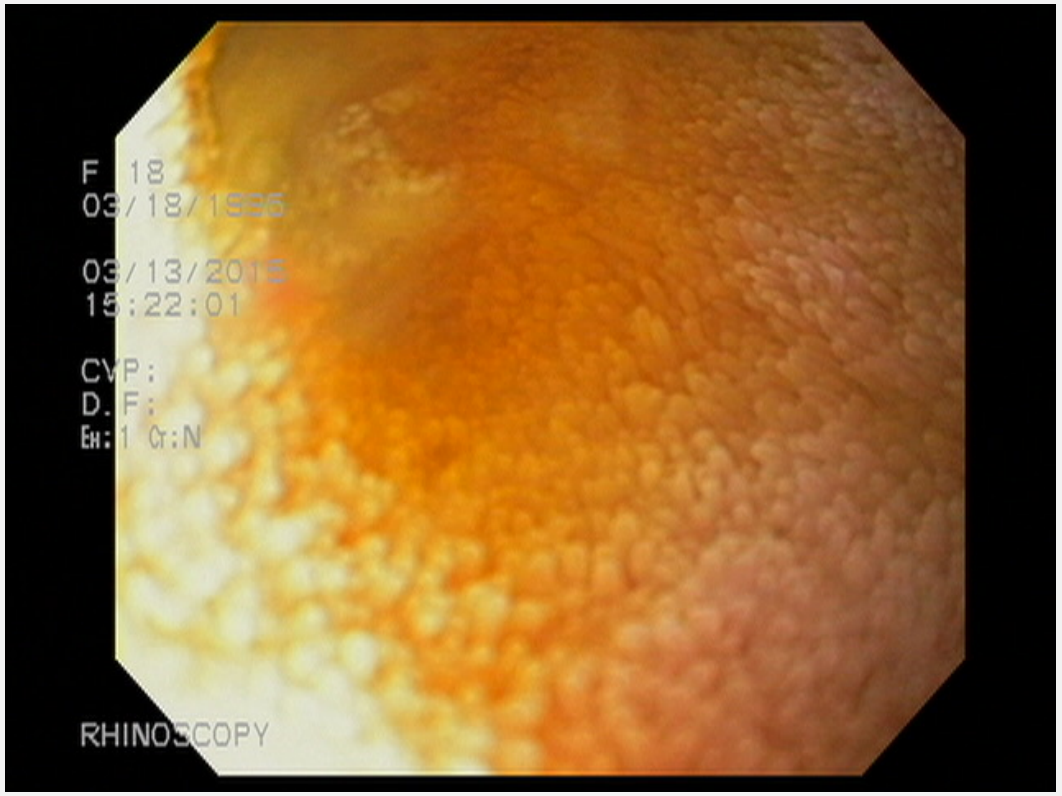
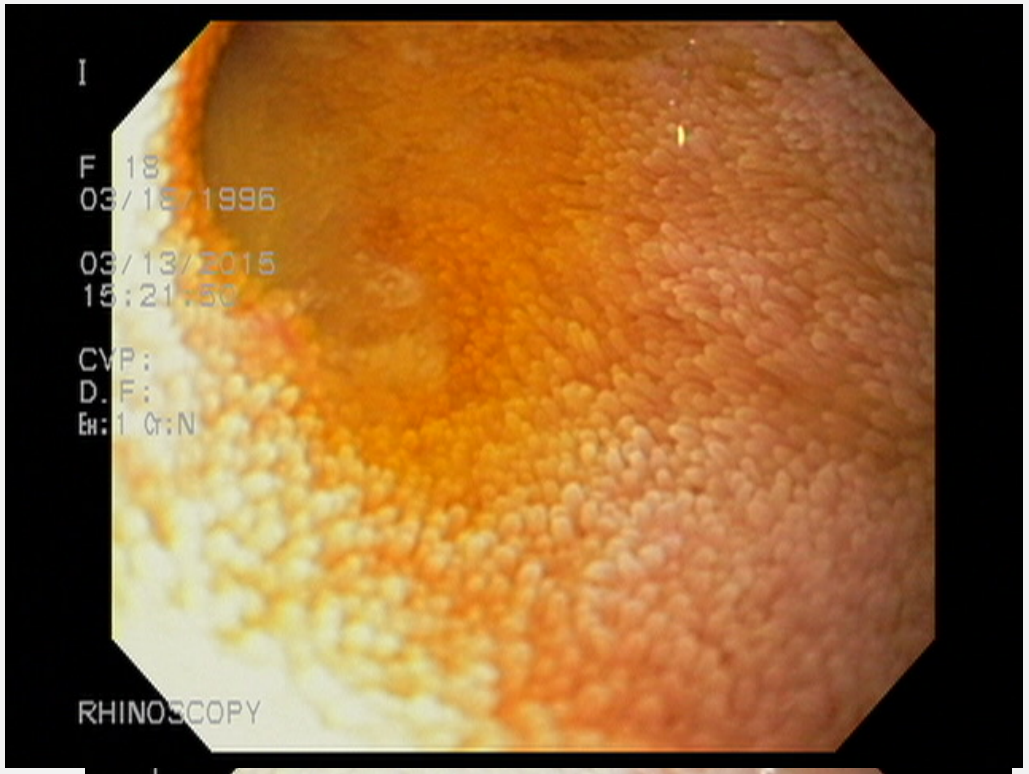


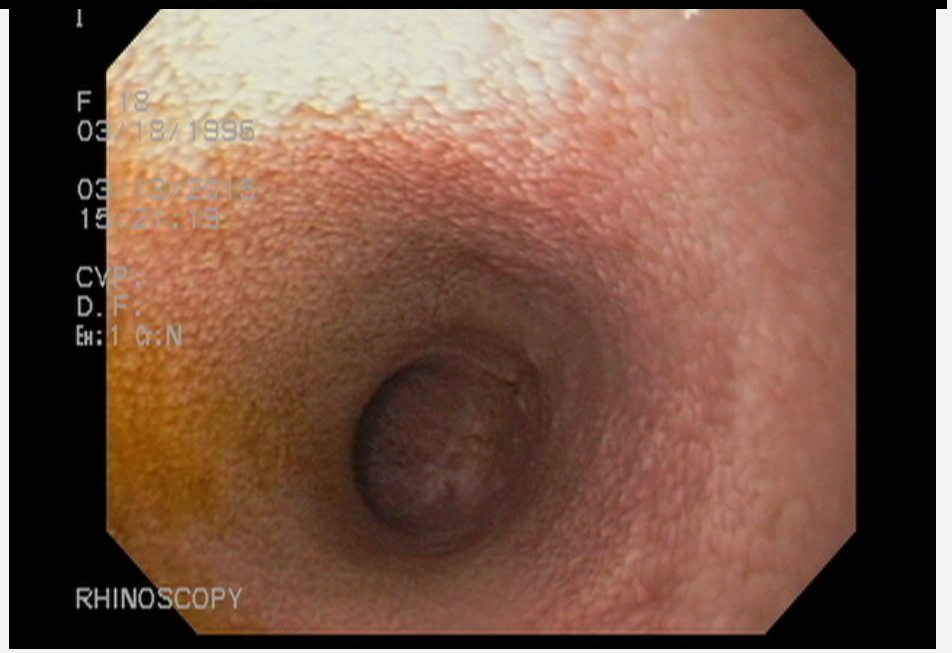
Figure 4-8 A, Advance of the endoscope through the pylorus. B, The endoscope tip is wedged against the wall of the most proximal aspect



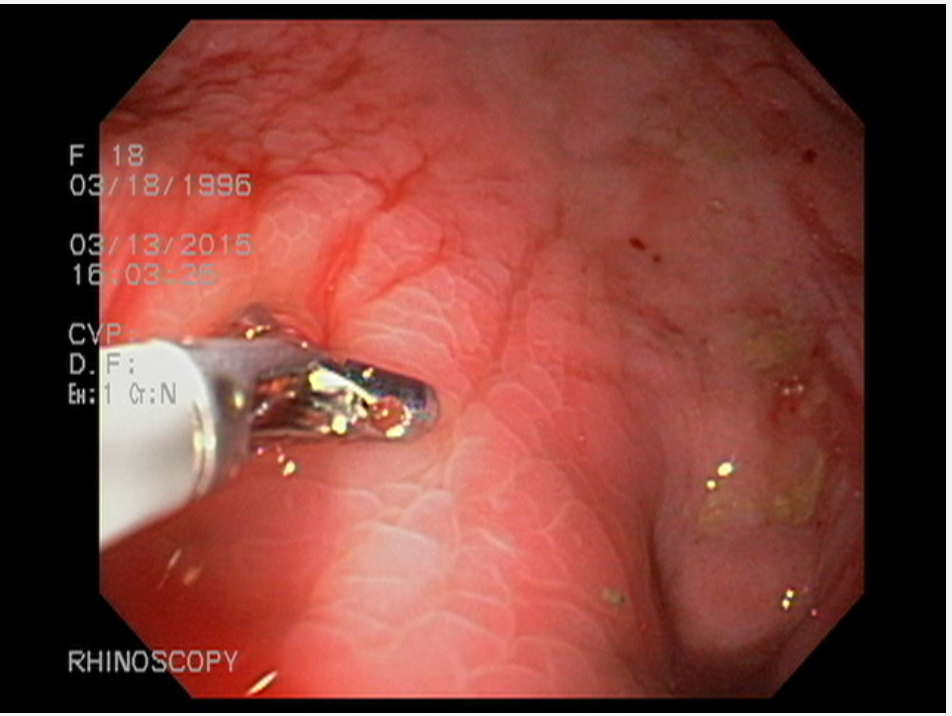






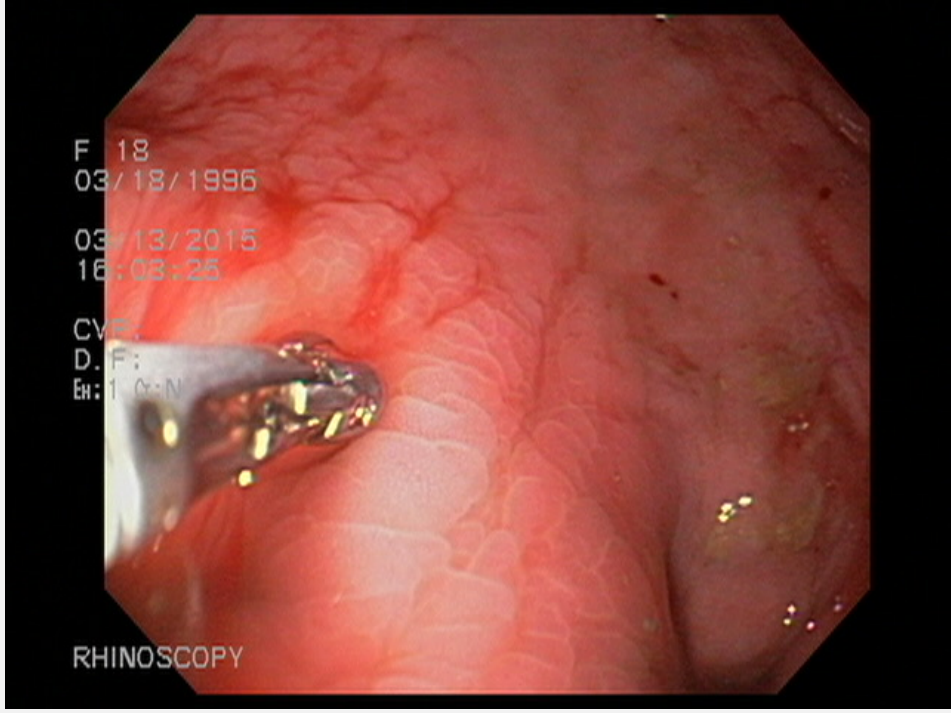


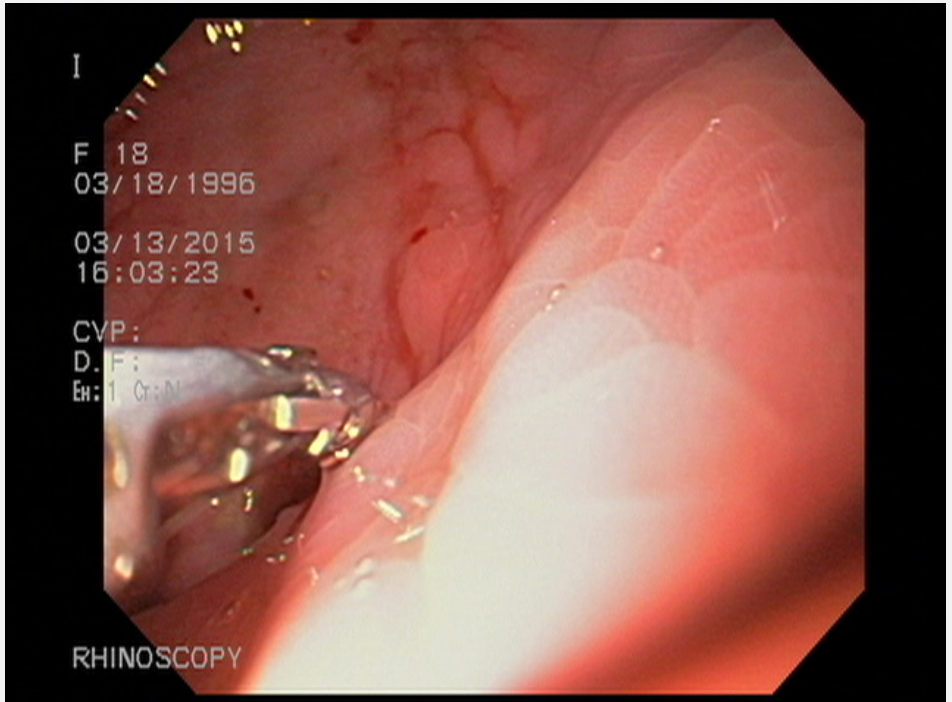
Duodenum:
Top Left – villi in the proximal duodenum
Top Right – villi near the duodenal flexure
Bottom Right – view down the descending duodenum



We always biopsy 4 regions:

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

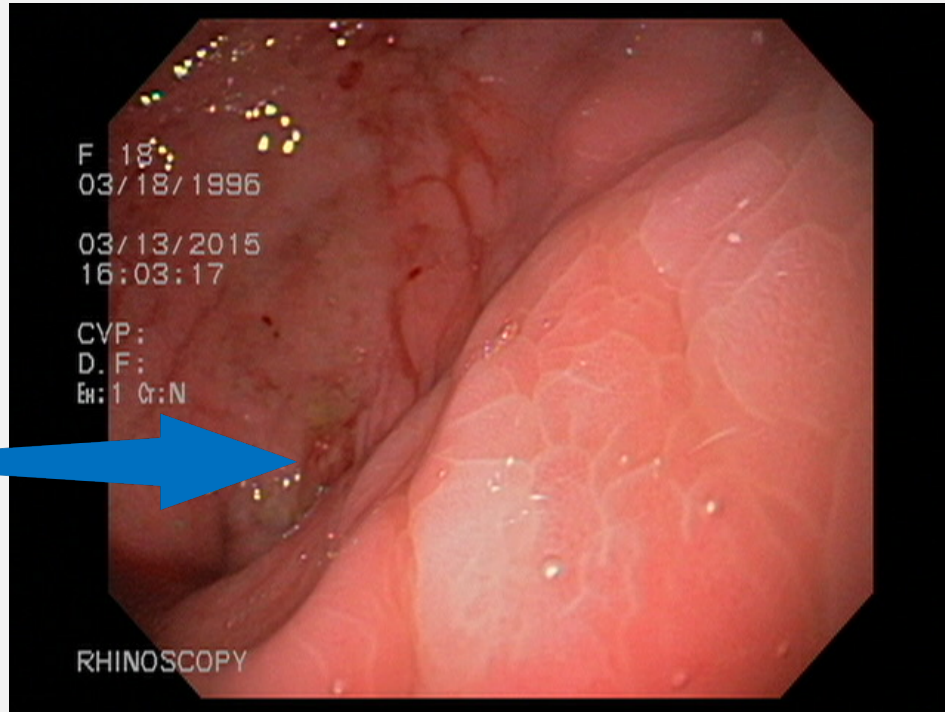




Biopsy forceps are quite small:

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

Biopsy site



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

CBC on Admission

Hematology

5/21/20 **5:51 PM**

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/µL
Reticulocyte Hemoglobin	26.9	22.3 - 29.6 pg
WBC	**29.81**	**5.05 - 16.76 x10^9/L** H
% Neutrophils	89.5	%
% Lymphocytes	6.8	%
% Monocytes	3.4	%
% Eosinophils	0.1	%
% Basophils	0.2	%
Neutrophils	**26.68**	**2.95 - 11.64 x10^9/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 x10^9/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 %

Why do we care about urine protein??

Chemistry

5/23/20 **11:25 AM** **5/21/20** 8:06 PM

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

Chemistry

5/24/20 **12:02 PM** **5/23/20** 11:25 AM **5/21/20** 8:06 PM

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	
a. Erosive	
Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)	Inflammatory bowel diseases (lymphoplasmacytic, eosinophilic, granulomatous)
Infections: *Giardia*, *Clostridium*, *Campylobacter*, *Salmonella*, *rotavirus*, *Whipple's disease*, intestinal tuberculosis	Infections: *Parvovirus*, *Clostridium*, *Campylobacter*, *Salmonellosis*, *Histoplasmosis*, *Schistosomiasis (Heterobilharzia americana)*
Neoplasia	Neoplasia
Nonsteroidal enteropathy	Nonsteroidal enteropathy
b. Non-Erosive	
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	
2. Infectious	
Lymphatic filariasis	Lymphatic filariasis (RARE)
	Hookworms
	Strongyloides stercoralis
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.

Received: 16 February 2018 | Accepted: 30 November 2018
DOI: 10.1111/jvim.15406
Journal of Veterinary Internal Medicine Open Access
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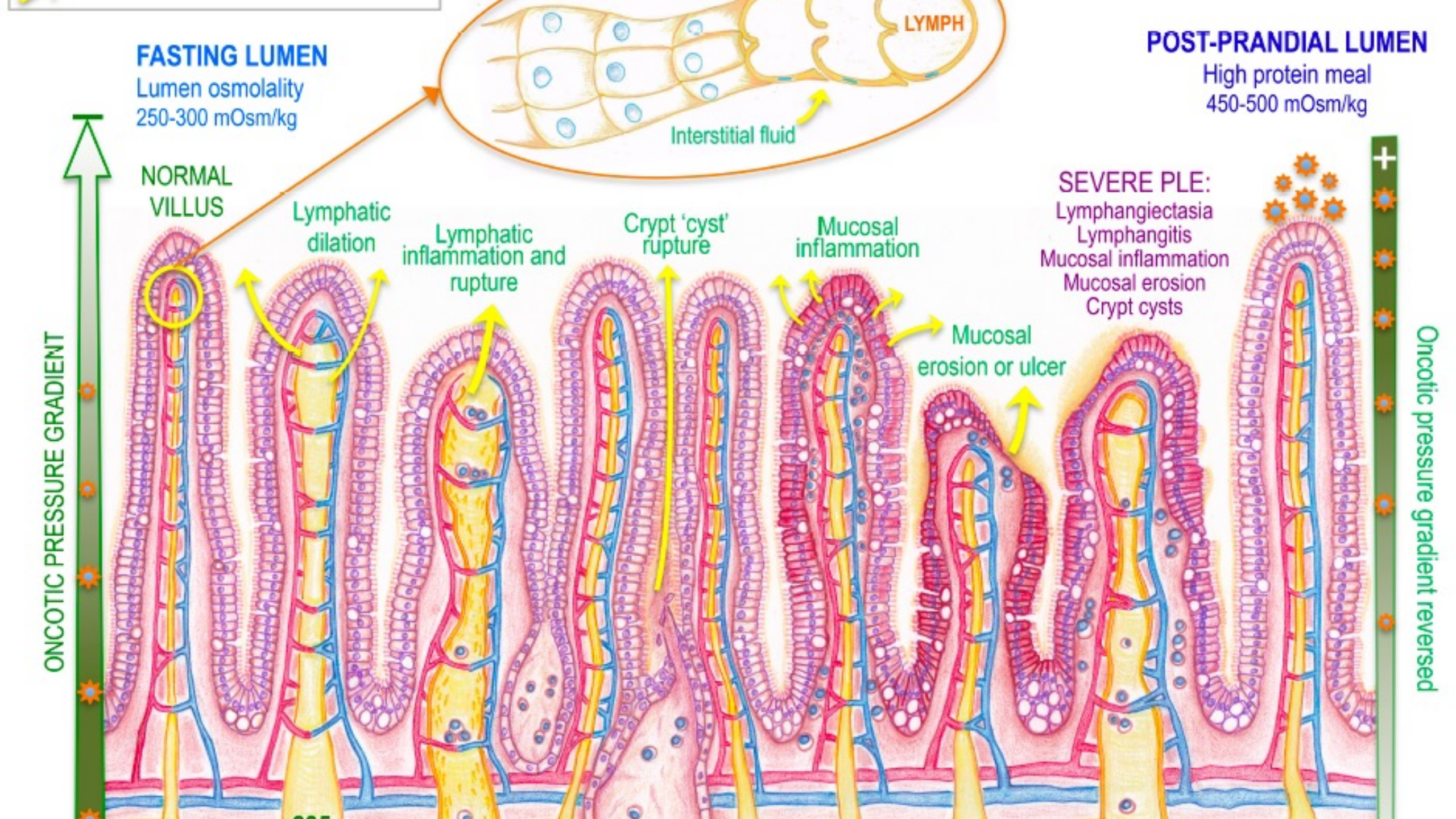
REVIEW

Comparative pathophysiology and management of protein-losing enteropathy

Melanie D. Craven[1] | Robert J. Washabau[2]

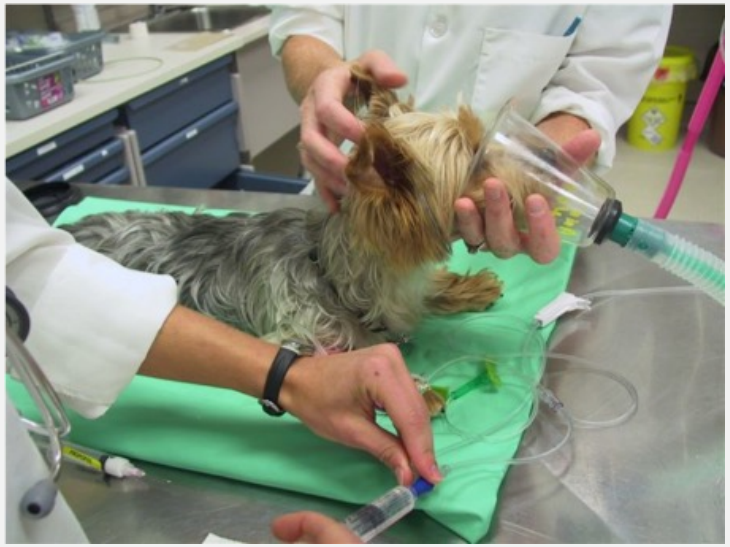

FASTING LUMEN
Lumen osmolality
250-300 mOsm/kg
LYMPH
Interstitial fluid
POST-PRANDIAL LUMEN
High protein meal
450-500 mOsm/kg
NORMAL VILLUS
Lymphatic dilation
Lymphatic inflammation and rupture
Crypt 'cyst' rupture
Mucosal inflammation
Mucosal erosion or ulcer
SEVERE PLE:
Lymphangiectasia
Lymphangitis
Mucosal inflammation
Mucosal erosion
Crypt cysts
ONCOTIC PRESSURE GRADIENT
Oncotic pressure gradient reversed
+

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 PLE

Received: 16 February 2018 | Accepted: 30 November 2018
DOI: 10.1111/jvim.15406

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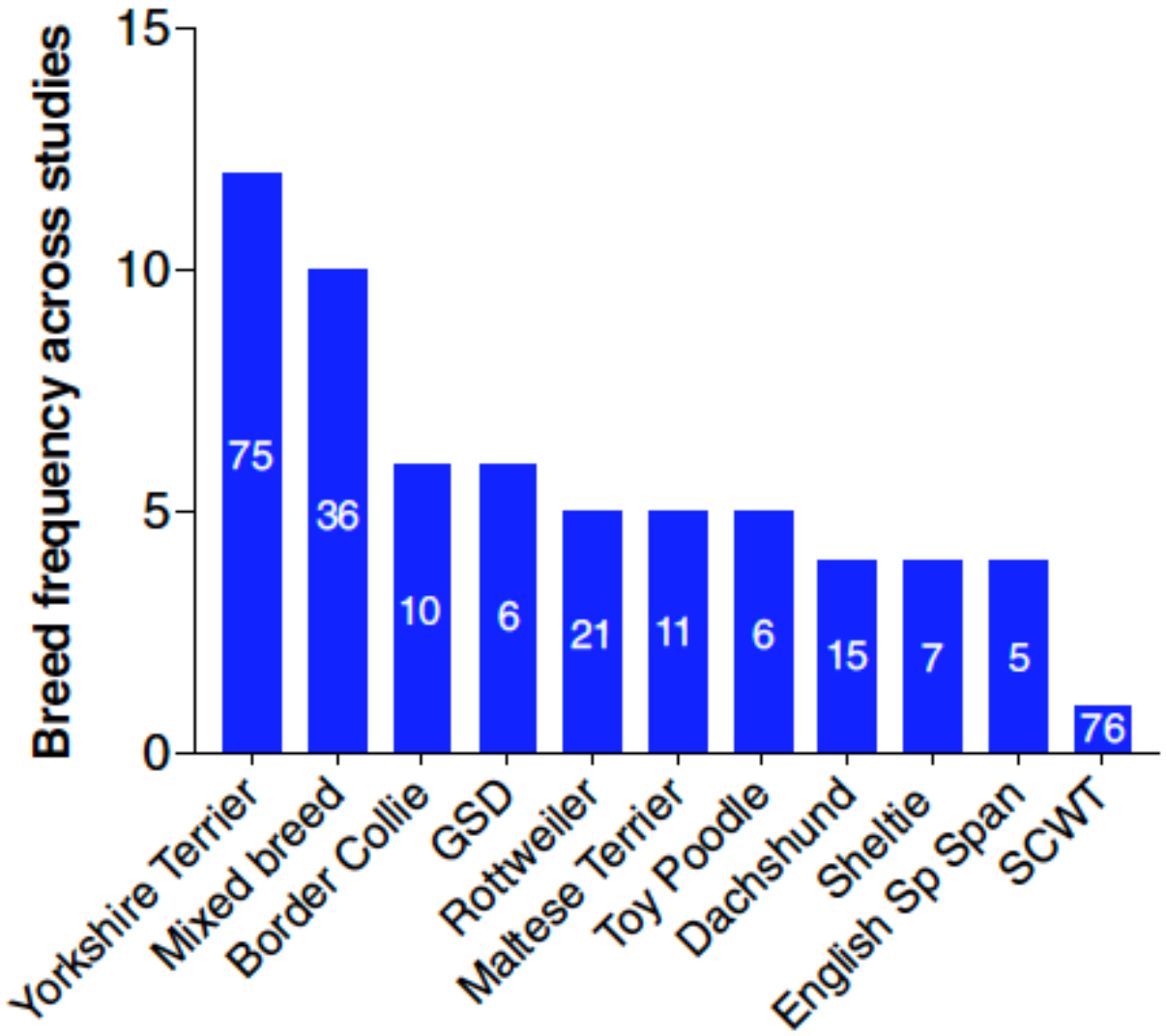


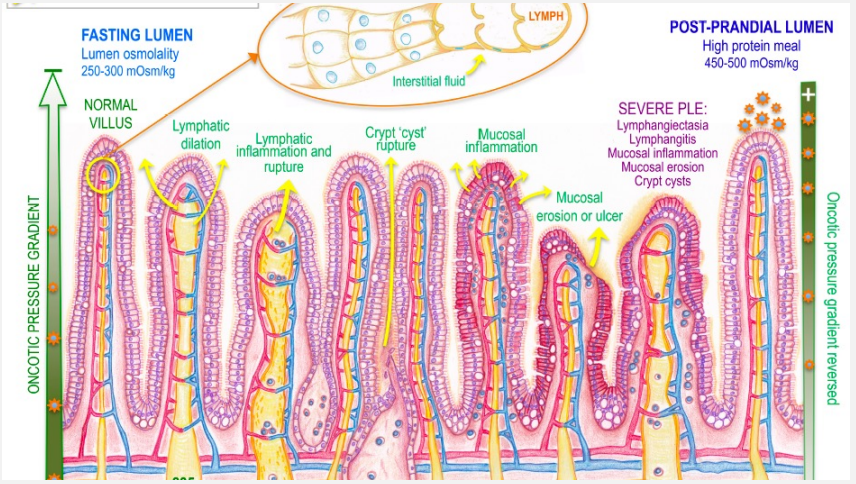
FIGURE 4 Breed frequencies represented across canine PLE publications; numbers on bars indicate the number of dogs within the breed.[12,13,49–69] PLE, protein-losing enteropathy

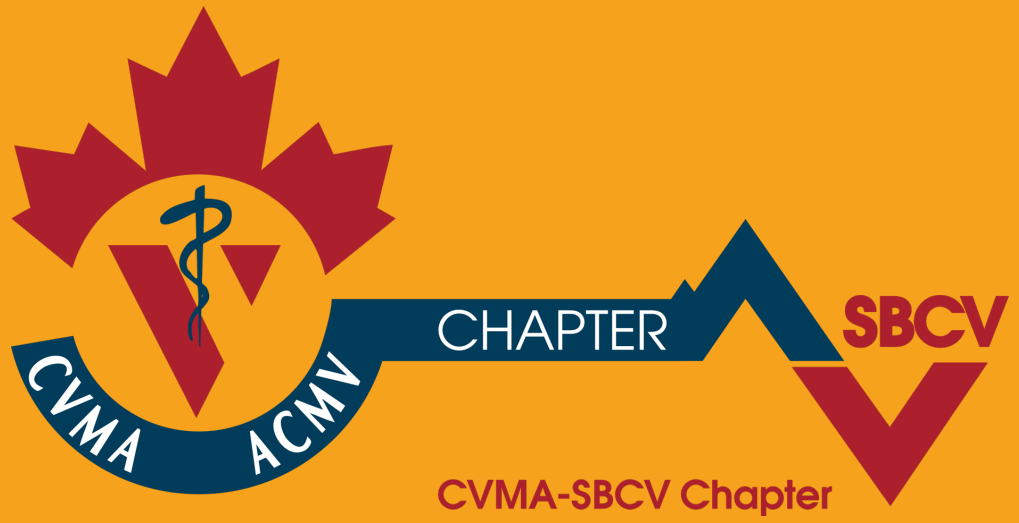
PLE - PROGNOSTIC FACTORS

- 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 Terries 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