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**ADVANCE2025**

Ok, it's 2025 –  
Do We Finally Have A Perfect Way To  
Differentiate IBD vs. GI Lymphoma

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Ok, it's 2025  
Do We Finally Have A  
Perfect Way To  
Differentiate IBD vs.  
GI Lymphoma

Marnin Forman DVM, DACVIM



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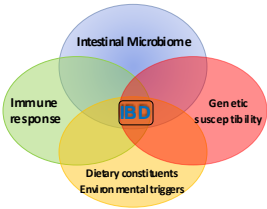
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### What is Chronic Enteropathy?

- GI signs > 3 weeks
- Extra-GI, metabolic and infectious causes ruled out
- ✓ Inflammatory bowel disease (IBD)
- ✓ Low-grade intestinal T-cell lymphoma (LGITL)



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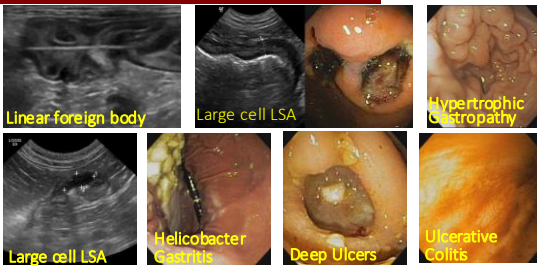
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## Who Cares? Just Give Them Pred




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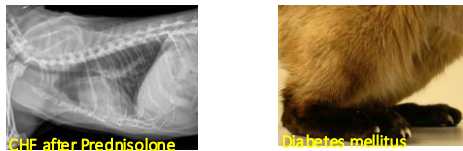
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## Who Cares? Just Give Them Pred



**Multidrug resistance LSA in Cats??**  
 Res Vet Sci 2021; 5(4): 138-176-187  
 doi: 10.55195/rvsc.2021.06.074. Epub 2021 Jun 15.  
 Effect of prednisone pre-treatment on cat lymphoma cell sensitivity towards doxorubicin, cyclophosphamide, vincristine, and mitoxantrone.  
 Jacek Hasiak<sup>1</sup>, Beata Kici<sup>2</sup>, Jacek Adam Matusz<sup>3</sup>, Barbara Sokoł<sup>4</sup>, Jolanta Tasiniak<sup>5</sup>, Urszula Walczak<sup>6</sup>, Beata Wroblewska<sup>7</sup>  
**Abstract**  
 Corticosteroid administration prior to the application of chemotherapy in small animal lymphoma patients is a concern, as it is discussed to negatively influence the therapeutic outcome due to corticosteroid-induced drug resistance. Using feline lymphoma cell lines F1<sup>+</sup> and M14 we have shown that prednisone pre-treatment alters the susceptibility of these cells towards doxorubicin or vincristine treatment in vitro. The observed effect was negative as for the binding potential and it was cell line and drug concentration or vincristine dependent. Furthermore, increase in mRNA expression of selected proteins with multidrug resistance potential (MDR1, BCRP, LRP, MTT) was observed after prednisone pre-treatment. Administration of chemical inhibitors of these proteins did not lead to reversal in sensitivity of tested cell lines to doxorubicin or vincristine.

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## IBD/LPE vs. LGITL

- Signalment  
 LPE 1.3 to 16y (median 8y), LGITL 4 to 20y (median 13y)  
 ≤8y LGITL is uncommon  
 Breed, gender and neuter status: doesn't help
- Medical history  
 Common signs of weight loss, inappetence vomiting  
 Clinical signs LPE median 107d, LGITL median 365d  
 No useful cutoff

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### IBD/LPE vs. LGITL



Exocrine pancreatic insufficiency

- Physical examination  
Diffusely thickened bowel loops: doesn't help
- CBC, chemistry panel, T4, FeLV/FIV, Urinalysis, Fecal
  - Microcytic anemia **LGITL** more common?
  - Hypoalbuminemia: If severe **LGITL** more common, If present with **IBD**, negative prognostic indicator
  - Elevated ALT: Significantly ↑ in **LGITL** 14% vs. **LPE** 0%  
Concern concurrent disease ± more severe disease

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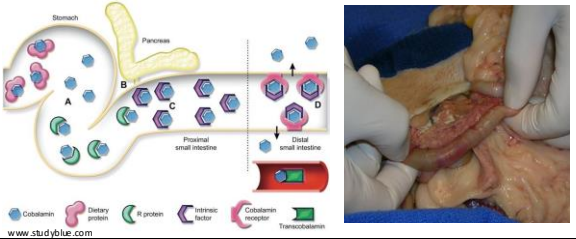
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### IBD/LPE vs. LGITL

Vitamin B12, folate levels, Pancreas-specific lipase ± TLI



www.studyblue.com

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### IBD/LPE vs. LGITL

Vitamin B12, folate levels, Pancreas-specific lipase ± TLI

- Vitamin B12
  - Both can have hypcobalaminemia, prevalence ↑ **LGITL**
  - ↑ refractoriness **IBD** treatment dogs / cats
  - Consider measuring Methylmalonic acid if low normal
- Folate levels
  - Hypofolatemia & hyperfolatemia are present in CE cats
  - If >15.5 μg/L 80% sensitivity 100% specificity **LGITL** in cats
- Pancreas-specific lipase
  - If ↑ Spec cPL / fPL & **IBD**, negative prognostic indicator

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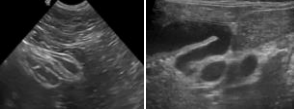
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### IBD/LPE vs. LGITL Abd. Ultrasound

<p><b>WHAT NOT TO MISS</b></p> <ul style="list-style-type: none"> <li>• GI masses</li> <li>• Foreign bodies</li> <li>• Pancreatitis</li> <li>• Hepatobiliary diseases</li> </ul>	<p><b>WHAT TO LOOK FOR</b></p> <ul style="list-style-type: none"> <li>• Wall thickness                             <ul style="list-style-type: none"> <li>✓ Stomach (D) ≤ 0.6cm (C) ≤ 0.3cm</li> <li>✓ SI (D) ≤ 0.4-0.6cm (C) ≤ 0.3cm</li> <li>✓ U (D,C) 0.1-0.2cm</li> </ul> </li> <li>✓ Peri-intestinal echogenicity</li> <li>✓ Layer distinction</li> <li>✓ Peristaltic activity (3-5x/min)</li> <li>✓ Luminal contents &amp; diameter</li> <li>✓ Adjacent lymph nodes</li> <li>✓ Ascites</li> </ul>
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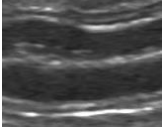
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### IBD/LPE vs. LGITL Abd. Ultrasound



1. Mucosa surface
2. Mucosa
3. Submucosa
4. Muscularis propria
5. Subserosa-serosa



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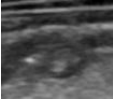
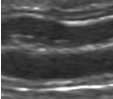


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### IBD/LPE vs. LGITL Abd. Ultrasound

Stomach	Duo. / Jejun.	<b>Layer</b>	Ileum	Colon
		<ol style="list-style-type: none"> <li>1. Mucosa surface</li> <li>2. Mucosa</li> <li>3. Submucosa</li> <li>4. Muscularis propria</li> <li>5. Subserosa-serosa</li> </ol>		

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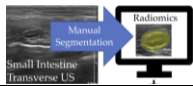
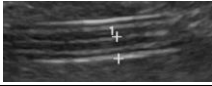


## IBD/LPE vs. LGITL Abd. Ultrasound

### IS THE SEGMENT IBD/LPE or LGITL

Ultrasound can not tell you, BUT it can help prioritize one condition over another. For **LGITL\***

- ✓ Significantly ↑ thickness of the muscularis propria or mucosa ± jejunal mucosal wall (median, 1.4 mm; range, 0.7-2.3 mm) ± jejunal lymph nodes (median, 6.7 mm; range, 2.9-12 mm, also rounder and hypoechoic)
- ✓ Mild abdominal effusion in cats with CE



\* Not Closer with AI  
53% accuracy

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## IBD/LPE vs. LGITL Biopsies

Should I biopsy:

- Severity of signs? Hypoalbuminemia? Hypocobalaminemia?
- Ultrasound findings: Thickness? Segment ± Layer involved?
- Presumptive vs. Targeted therapy?
- Failed empirical therapy to confirm the diagnosis
  - Classify the type of IBD, evaluate for architectural changes (i.e., crypt distortion and villus blunting)
  - Eliminate non-IBD disorders, in particular, neoplastic or infectious enteropathies or lymphangiectasia

**IN WHAT ORDER** → Jejunum, ileum, duodenum, stomach, colon

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## IBD/LPE vs. LGITL Biopsies **JUST DO IT.**

How should I biopsy- Surgical vs. Endoscopic?

- Surgical
  - ✓ Abdomen is already open, full-thickness, **6mm punch**
  - ✓ Concern for Jejunal disease or Leiomyositis?
  - ✓ Prior endoscopic biopsy findings do not correlate with clinical picture




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## IBD/LPE vs. LGITL Biopsies JUST DO IT.

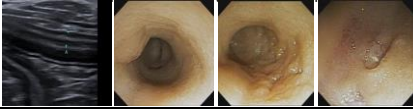
How should I biopsy- Surgical vs. Endoscopic?

→ Endoscopic

- ✓ Less invasive option, better option (more mucosa?)
- ✓ Need to start steroids rapidly
- ✓ Endoscopic appearance provides better prognostic info than histo?

→ Technique doesn't matter?

- ✓ Apparent involvement of the submucosa or muscularis (LGITL infiltration generally is located in the lamina propria)



**Low-grade Intestinal T-cell lymphoma (LGITL)**

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## IBD/LPE vs. LGITL Biopsies



### Diagnostic Endoscopy

→ Assess granularity, friability, and erosions, guided biopsies

→ More difficult to biopsy the SI vs Stomach!

→ Transcolonic ileoscopy + standard upper GI tract endoscopy?

- If low cobalamin levels ± abnormal ultrasonographic findings
- Independent of localization of the SI disease ↑ likelihood of diagnosing LGITL (44% of cats based solely on an ileal sample)

→ In dogs, greater ileal damage with > ↓ serum cobalamin\*

- Histo: Villus atrophy, crypt dilatation, epithelial injury, intraepithelial lymph
- Ileal endoscopy: Friability
- Cobalamin concentration: Severely low

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\* J Vet Intern Med. 2022;May;38(3):957-965

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## IBD/LPE vs. LGITL Diagnostic Endoscopy


Proximal Duodenum



Mid Duodenum



Ileum



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### IBD/LPE vs. LGITL Biopsies

How do I Optimize Endoscopic Biopsies\*



- ✓ Using a 2.8mm channel biopsy forceps with larger > smaller cups
- ✓ Tissue fixation using a non-absorbent sponge or filter paper is better than free-floating
- ✓ Quality / Number of endoscopic biopsies significantly impacts results
  - Minimum 6 adequate quality duodenal & 3-5 ileal biopsies collected in cats
  - Ideal more, since they might not be 'adequate' 10-15 biopsies are best

→ Get more in older cats, smaller cups biopsies, freefloating

**HIGH QUALITY**

\* J Vet Intern Med. 2025 Mar 8;39(2):e70069  
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### IBD/LPE vs. LGITL Histopathology IBD

Semiquantitative estimate of type & degree of cellular infiltrate

- ✓ Eosinophilic, neutrophilic, lymphoplasmacytic, granulomatous
- ✓ Focal to diffuse distribution
- ✓ Subjectively categorized as normal, mild, moderate, or severe

**HOWEVER**, most studies (n=166) revealed NO significant association

- ✓ Severity of clinical signs
- ✓ Biomarkers of disease
- ✓ Response to treatment
- ✓ Outcome

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### IBD/LPE vs. LGITL Histopathology IBD

Mucosal architecture findings may prove to be more accurate

- ✓ Correlate with clinical severity, proinflammatory cytokines and categorization for IBD

World S.A. Vet. Association (WSAVA) GI Standardization Group

- ✓ 9 histologic features: cellular infiltrate AND intraepithelial lymphocytes, villous stunting & epithelial injury, crypt lesions, fibrosis & lacteal dilation [≠ goblet cell mucus content]
- ✓ "Substantial inconsistency" between pathologists despite the use of pictorial template because of differences in slide processing

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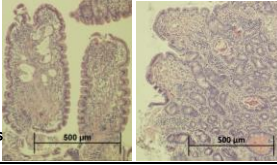
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### IBD/LPE vs. LGITL Histopathology IBD

- ✓ In cats with SI IBD, villus atrophy and fusion correlated with the severity of clinical signs
- ✓ In dogs with LI IBD, loss of mucus and goblet cells correlated with severity of inflammation



Prominent villus Lacteal Dilation

Crypt Effusion, Villus Blunting, Lymphocytes & Plasma Cells

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### IBD/LPE vs. LGITL Histopathology

Not IBD/LPE?

- Neutrophilic and/or granulomatous inflammation
  - ✓ Cytochemical 'special' stains (Gomori methenamine silver, periodic acid-Schiff, Gram, and modified Steiner stains)
  - ✓ Fluorescent *in situ* hybridization with a probe directed against eubacterial 16S ribosomal RNA (FISH)

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### Histopathology

IBD

**Polyclonal** lymphocytic infiltration lamina propria  
Lymphoplasmacytic enteritis (LPE)

LGITL

Monomorphic infiltration of lamina propria ± epithelium  
small, **Clonal** T lymphocytes

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## Histopathology

<p><b>IBD</b></p> <p><b>Polyclonal</b> lymphocytic infiltration lamina propria Lymphoplasmacytic enteritis (LPE)</p>	<p><b>LGITL</b></p> <p>Monomorphic infiltration of lamina propria ± epithelium small, <b>Clonal</b> T lymphocytes</p>
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← 60% of cats with LGITL have IBD →

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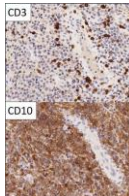
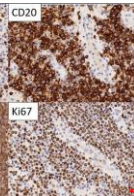
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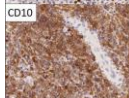
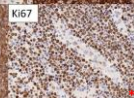
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## IBD/LPE vs. LGITL Histopathology

→ IBD/LPE vs. LGITL

- ✓ Stepwise diagnostic approach?
- Histopathology
- Immunohistochemistry
- PARR testing PCR for Antigen Receptor Rearrangement(PARR)

\*www.researchgate.net/figure/immunohistochemistry-the-large-cells-express-CD20-and-CD10-and-showed-high-Ki67

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## IBD/LPE vs. LGITL Immunohistochemistry

→ Mixed infiltrate implies the presence of antigenic stimulation during inflammation (suggestive of LPE).

→ LGITLs in cats generally: low expression of Ki-67, high expression of STAT5 & CD3+/CD56- cells.

- However, since concurrent LPE has been described in up to 60% of cases with LGITL, this technique does not allow for absolute differentiation.
- Also, chronic antigenic stimulation can lead to monoclonal proliferation of lymphocytes.

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## IBD/LPE vs. LGITL PARR



- ✓ Detects clonally expanded population of lymphocytes
- ✓ How accurate is it?

CATS	Sensitivity	Specificity	DOGS	Sensitivity	Specificity
T-Cell	89-95%	100%	T-Cell	~90%	~90%
B-Cell	68-70%	100%	B-Cell	~80%	~80%

- \* Diagnostic performance is different for different labs
- False **negative**: Non-assessed clonal rearrangements, mutations at the primer binding sites, large # of reactive lymphocytes
- False **positive** (pseudoclonal): Very low # of B or T lymphocytes, highly focused immunologic responses (E. canis, FIV) infection or chronic inflammatory intestinal disorders

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### Questions

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