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Acute Pancreatitis – Diagnosis & Management

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Financial Disclosure: Steiner

• Gastrointestinal Laboratory	Director
• IDEXX Laboratories	Paid Consultant
• Nutramax Laboratories	Paid Consultant
• ISK	Paid Consultant
• CEVA Animal Health	Paid Consultant
• Glycosbio	Paid Consultant
• Bond Pet Care	Paid Consultant
• Nutramax Labs, IDEXX Labs, CEVA, Siemens Healthineers	Paid Speaker
• Hill's Pet Care, Nutramax Labs	Grant Support

Financial Disclosure: Cridge

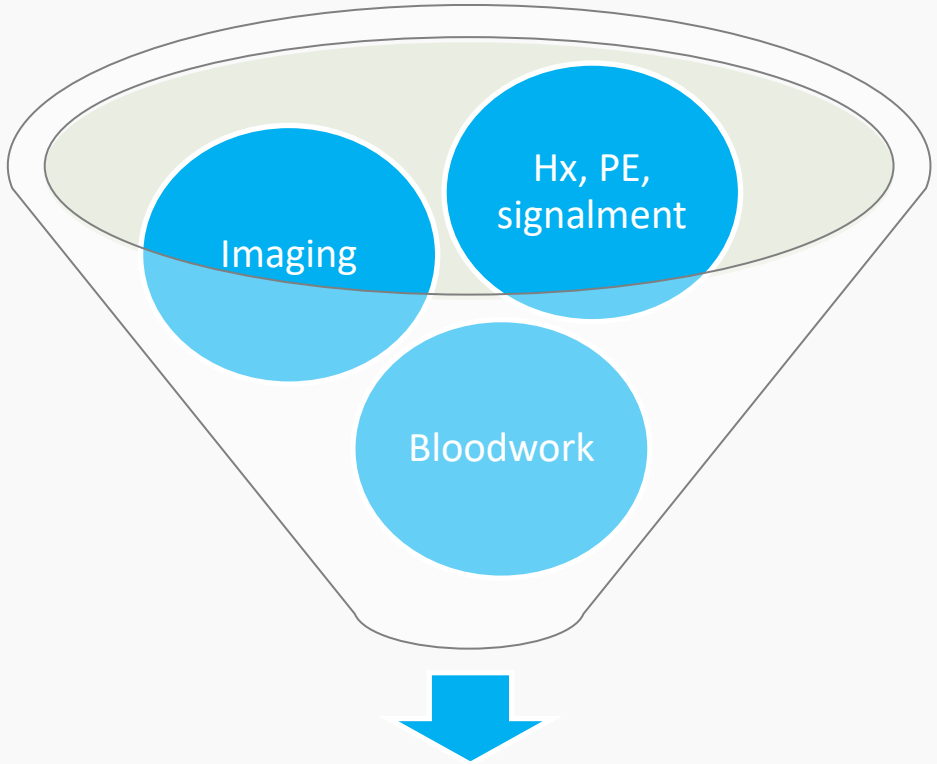
I have financial interest, arrangement or affiliation with:

Name of Organization	**Relationship**
CEVA Animal Health	Paid speaker, content developer, and recipient of research funding
Royal Canin	Paid speaker, and recipient of research funding (via CGS).
IDEXX Laboratories	Paid speaker

Pancreatic inflammation

- More common than previously believed
- Chronic disease more common than acute disease
- Some changes may be subclinical
- Some changes may not be clinically relevant

Diagnosis of Pancreatitis – Clinical Reference Standard



Clinician is the gold standard – great job security!

But we must be cognizant of limitations of each diagnostic tool to determine an optimal diagnosis.

The level of diagnostic confidence needed is likely also dependent on the clinical scenario

animals

MDPI

Article

Risk Factors and Clinical Presentation in Dogs with Increased Serum Pancreatic Lipase Concentrations—A Descriptive Analysis

Harry Cridge [1,*], Nicole Scott [2] and Jörg M. Steiner [2]

Table 3. Clinical signs reported in returned survey data from dogs with a serum cPLI ≥ 400 µg/L.

Clinical Sign	No. of Dogs Affected
Inappetence	92/148 (62%)
Diarrhea	78/148 (53%)
Vomiting	77/148 (49%)
Lethargy	67/148 (45%)
Nausea	52/148 (35%)
Abdominal pain or discomfort	48/148 (32%)
Regurgitation	15/148 (10%)
Other clinical signs	55/148 (37%)

Diagnostic Imaging

Enlarged, hypoechoic pancreas, with bright surrounding mesentery

The greater the no. of sonographic abnormalities the greater the diagnostic specificity (*)

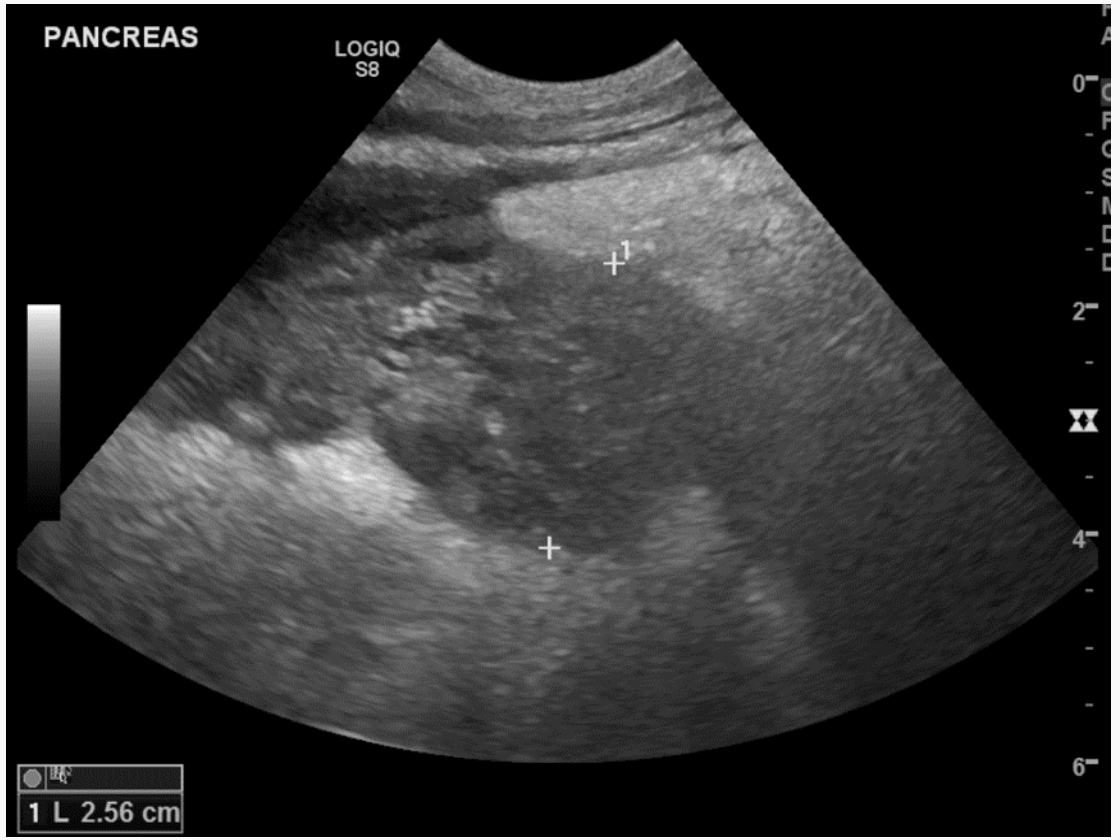


Image from Michigan State University

DOI: 10.1111/jvim.15693

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access
ACVIM American College of Veterinary Internal Medicine

Association between abdominal ultrasound findings, the specific canine pancreatic lipase assay, clinical severity indices, and clinical diagnosis in dogs with pancreatitis

Harry Cridge[1] | Alyssa M. Sullivant[1] | Robert W. Wills[2] | Alison M. Lee[1]

Diagnosis – Imaging

Prevalence of ultrasonographic gastrointestinal wall changes in dogs with acute pancreatitis: A retrospective study (2012-2020)

Joshua J. Hardwick[1,2] | Elizabeth J. Reeve[3] | Melanie J. Hezzell[1] | Jenny A. Reeve[1]

Concurrent GI wall changes are common (~ 50%) of dogs. #1 site: duodenum

Of those with changes:

~75% wall thickening
~60% abnormal wall layering

Do NOT confuse abnormal wall layering with neoplasia → may resolve after pancreatitis resolves.

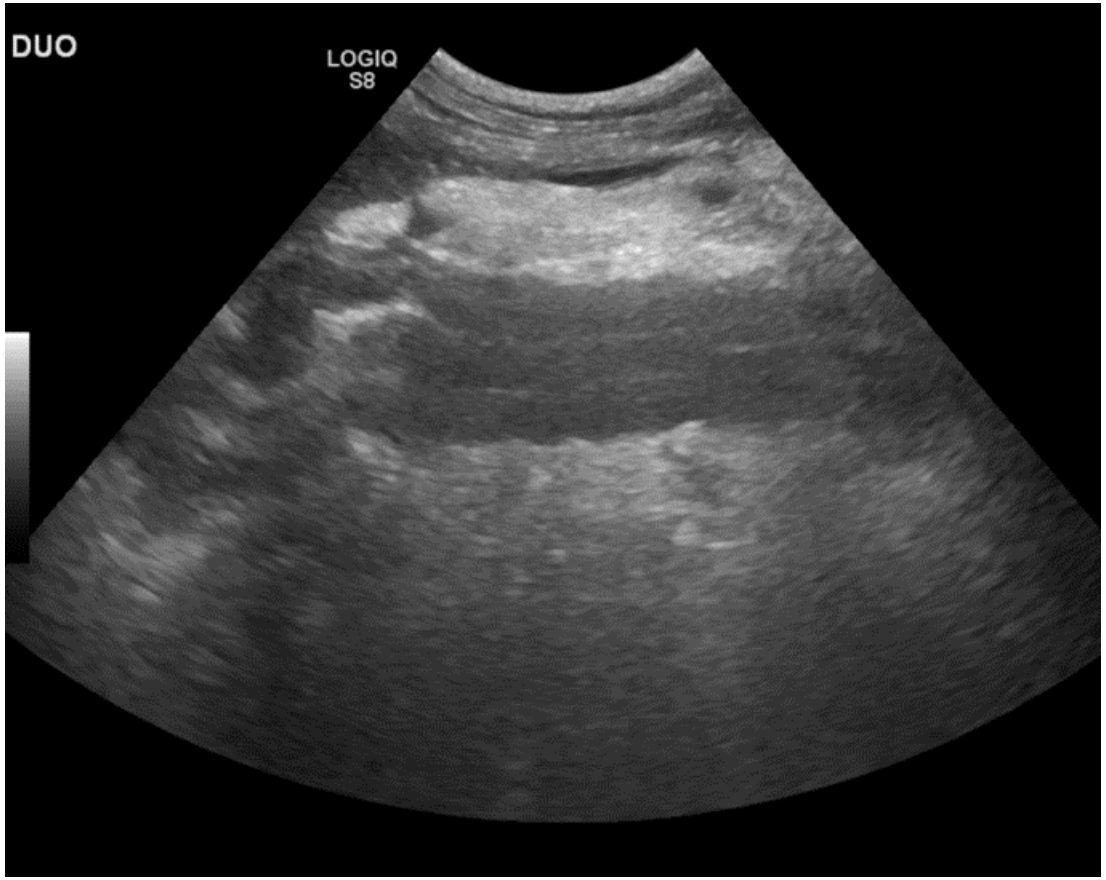


Image from Michigan State University

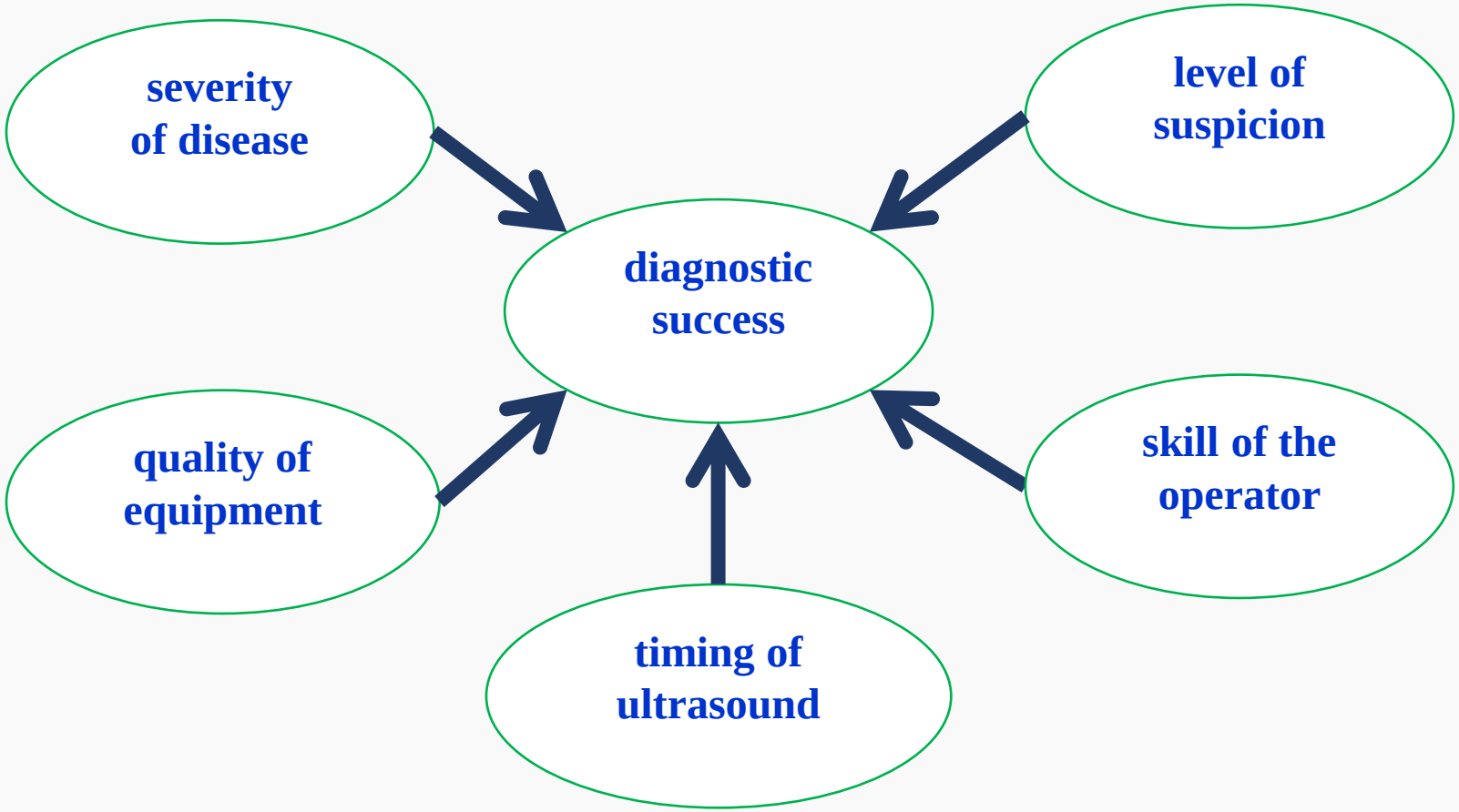
Diagnostic Imaging - Challenges

- Sensitivity is largely operator dependent and has been reported to be up to 68% in dogs
  - sensitivity lower with less severe disease
  - sensitivity lower with limited operator skill

- Specificity is limited by other conditions being associated with similar changes hyperplastic nodules
  - occur in up to 100% of older animals

- Pancreatic edema
- Peritoneal effusion

Ultrasound for the Diagnosis of Pancreatitis



One more comment … test results don't always agree

Evaluation of diagnostic and prognostic usefulness of abdominal ultrasonography in dogs with clinical signs of acute pancreatitis

ANIMALS
37 client-owned dogs with clinical signs of AP.

RESULTS
24 of 37 (64.8%) dogs had AUS findings of AP at hospital admission, whereas 10 had positive findings for AP on AUS within 2 days of hospitalization. Three (8%) dogs were AUS– but had serum cPL concentrations > 400 µg/L (ie, values considered diagnostic for AP). On the AUS severity index, 5 of 34 (14.7%) AUS+ dogs had mild findings, 18 (52.9%) AUS+ dogs had moderate findings, and 11 (32.4%) AUS+ dogs had severe findings. Severe findings were associated with a higher risk of death than mild and moderate findings. A significant association was found between canine acute pancreatitis severity scores and mortality rates.

CONCLUSIONS AND CLINICAL RELEVANCE
For dogs with clinical signs of AP, repeated AUS examinations during hospitalization should be performed, severe findings on the AUS severity index may indicate an increased risk of death, and serum cPL concentrations may increase earlier than findings on AUS of AP. (*J Am Vet Med Assoc* 2021;259:631–636)

JAVMA
JOURNAL OF THE AMERICAN VETERINARY MEDICAL ASSOCIATION

Imaging – AUS vs CT

Computed tomographic angiography and ultrasonography in the diagnosis and evaluation of acute pancreatitis in dogs

John M. French[1] | David C. Twedt[2] | Sangeeta Rao[2] | Angela J. Marolf[1]

Results: Ten of 26 dogs had heterogeneous contrast enhancement of the pancreas. Compared to US, CTA better identified portal vein thrombosis (P = .003). Patients with heterogeneous contrast enhancement had longer hospitalization (P = .01), including hospital stays for >5 days (P = .02), had more relapses, and were more likely to have portal vein thrombosis (P = .002). Patients with heterogeneous contrast enhancement had increased spec cPL (P = .006).

Conclusions and Clinical Importance: In comparison to US, CTA better identified dogs with more severe acute pancreatitis and those with portal vein thrombosis, factors that may predict longer hospitalization and increased risk of relapse. The presence of heterogeneous contrast enhancement and portal vein thrombosis may change therapy for patients with acute pancreatitis.

Image from Michigan State University

Times I Consider CT:

- OVERALL RARE
- Too much gas shadowing to visualize cranial abdomen
- Dog has refractory abdominal pain (looking for PV clot)

French et al. *J Vet Intern Med.* 2019; 33:79

Clinical Pathology

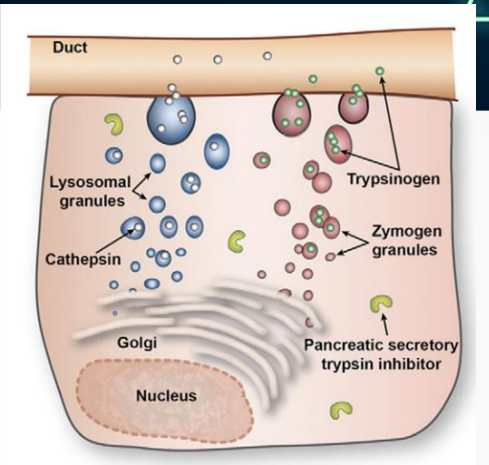
- CBC and Serum Chemistry
  - Variety of changes can be observed
  - None are specific for pancreatitis

→ however, they are crucial to evaluate the patient for systemic complications and to help screen for alternate DDx

Diagnosis – Pancreatic Lipase

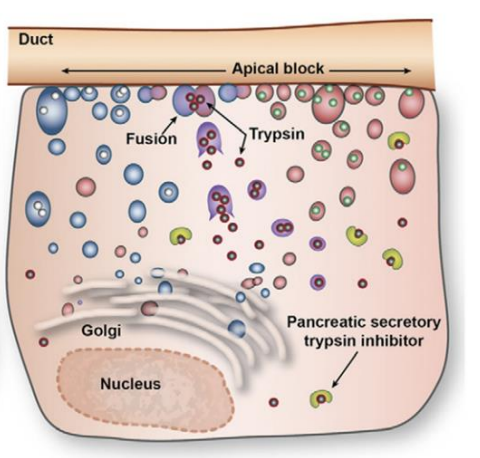
Normal physiology

- ~99% pancreatic lipase released into GI tract
- <1% diffuses from basolateral aspect into circulation



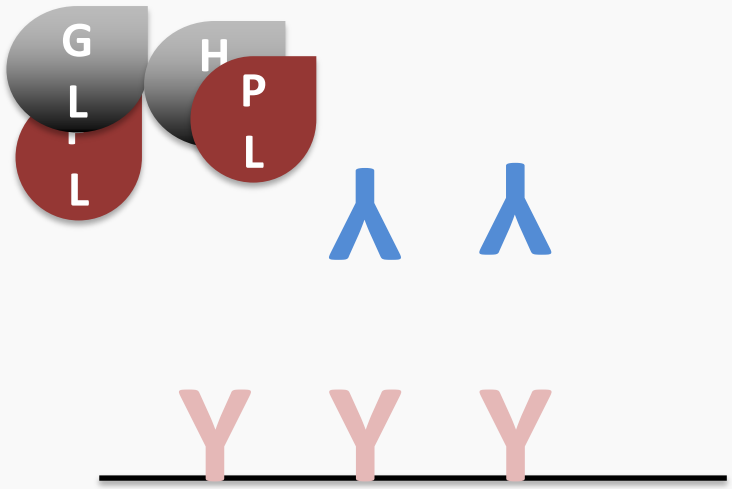
Pancreatitis

- Apical secretion blocked
- > pancreatic lipase released into circulation
- Measurement of pancreatic lipase useful

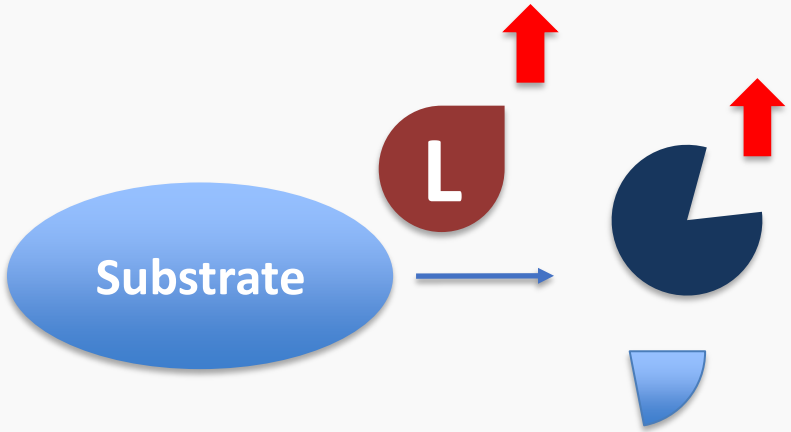


Diagnosis – pancreatic lipase

Immunological



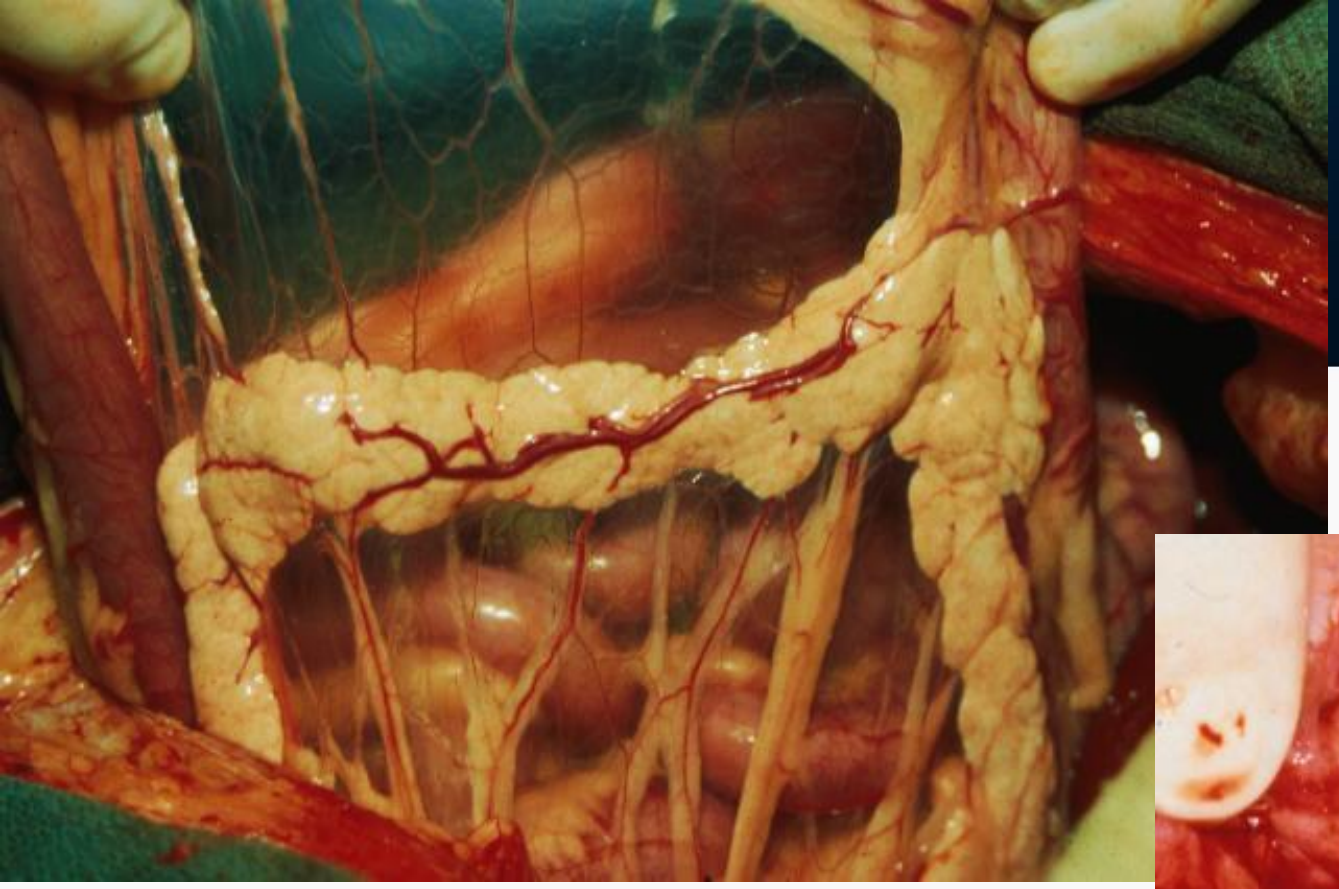
Catalytic

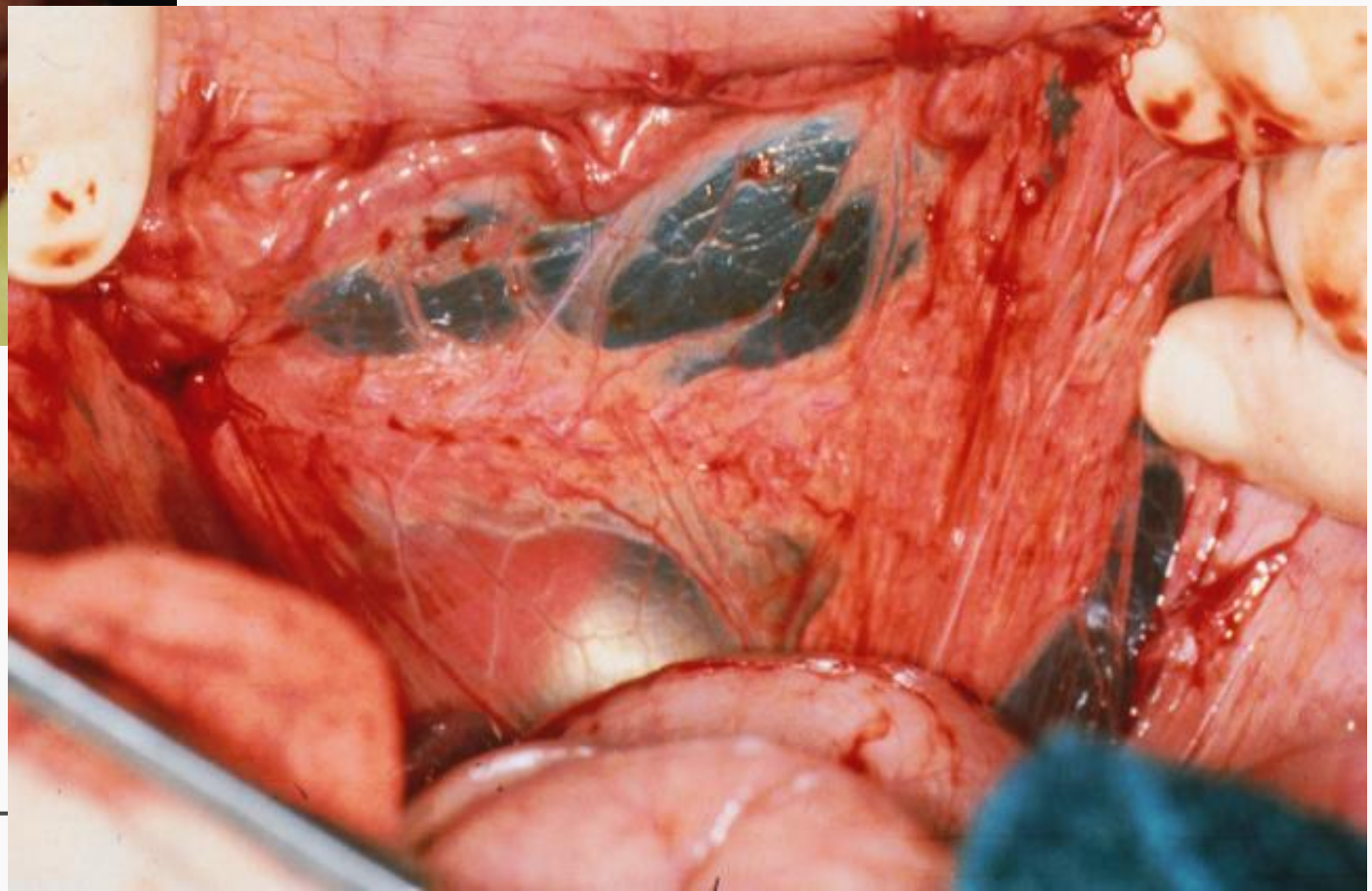


Lipase Activity can be Measured by Different Assays

- Even if assays use the same substrate, they may produce completely different results
  - ➢assay conditions are crucial
    - co-factors added
    - temperature
    - analyzer
    - pH
    - many others

Specificity of lipase assays





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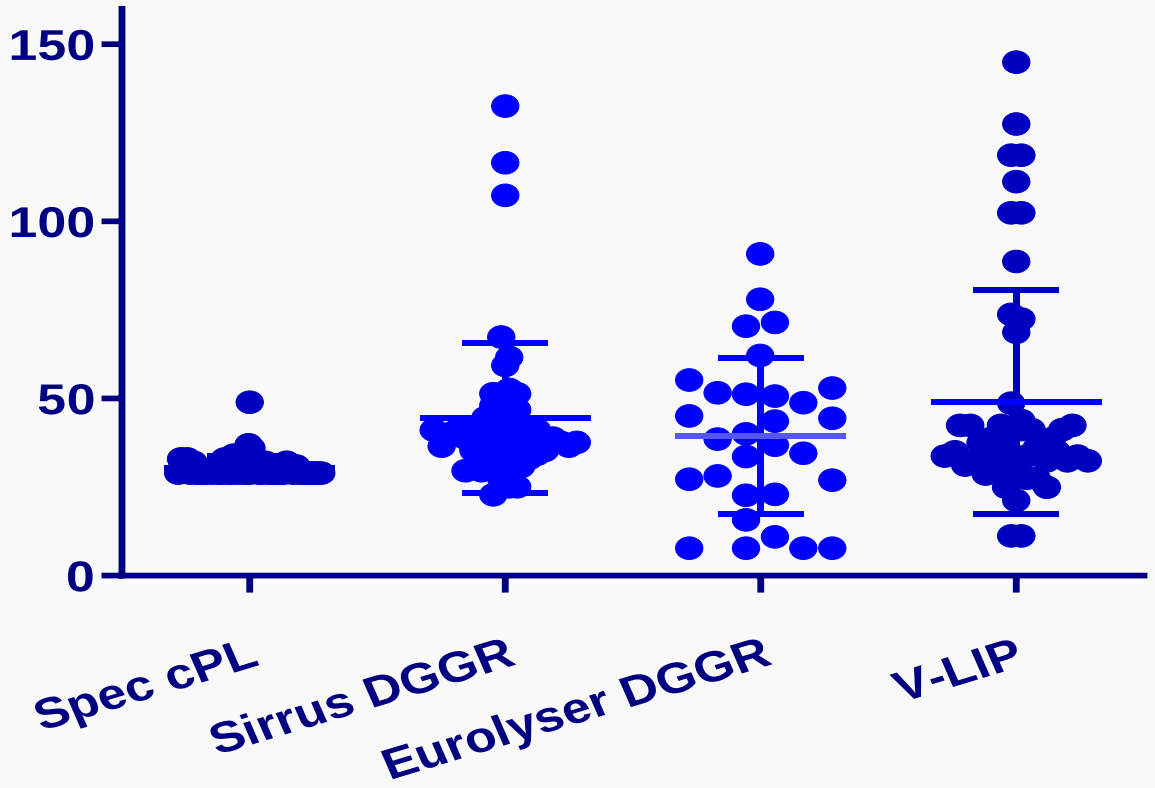
Assay Comparison



Spec cPL is the most specific assay for the measurement of pancreatic lipase

Where is lipase activity coming from?

- extra-pancreatic lipases
- PLRP2
- esterases
- proteinases
- hemoglobin

DGGR Study

- 30 client-owned dogs
- presented to the Veterinary Teaching Hospital for vomiting, diarrhea, or abdominal pain
- diagnosis of pancreatitis in 15 dogs based on clinical history, clinical signs, and ultrasonographic findings

Graca et al. 2005

Sensitivity & Specificity

	Sensitivity	Specificity
1,2 DiG assay	60%	73%
DGGR assay	93%	53%

Graca et al. 2005

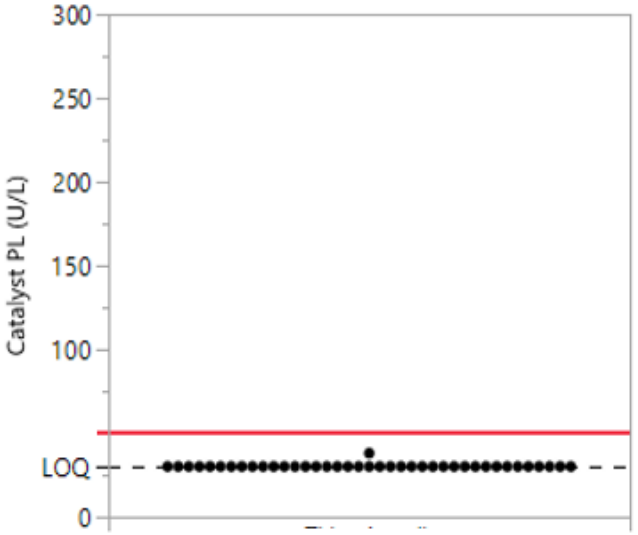
Catalyst PL by IDEXX Laboratories

- New DGGR-based in-house assay for the catalyst analyzer
- 1st DGGR-based lipase assay on a dry- chemistry analyzer
  ⇨proprietary technology to keep DGGR stable
- 1st DGGR-based lipase assay that appears to be specific for the measurement of pancreatic lipase
  ⇨proprietary technology

Catalyst PL by IDEXX Laboratories

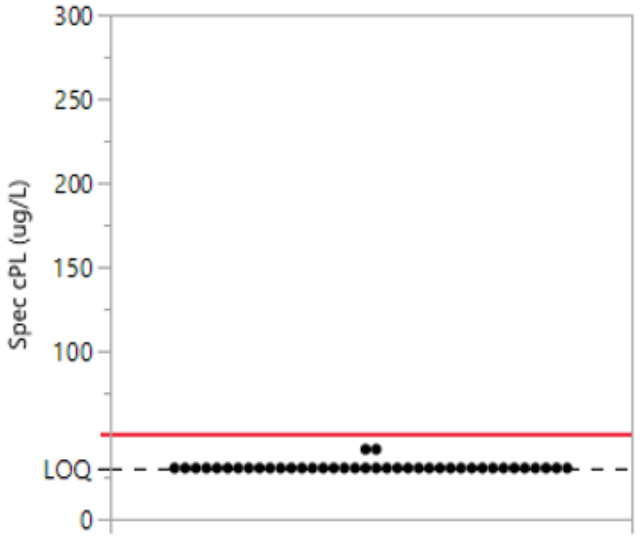
- Internal analytical validation has been completed
- External analytical validation has been completed
- Provides a numerical result that has been aligned with the Spec PL assays
- Ideal for patients with acute clinical signs that require immediate and accurate results

Specificity in Dogs with PAA



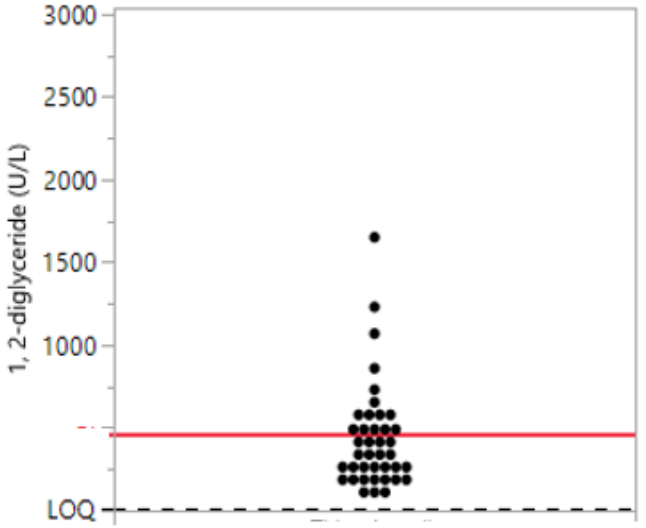
Catalyst PL

3 samples > 30 U/L
0 samples > 50 U/L



Spec cPL

5 samples > 30 ug/L
0 samples > 50 ug/L

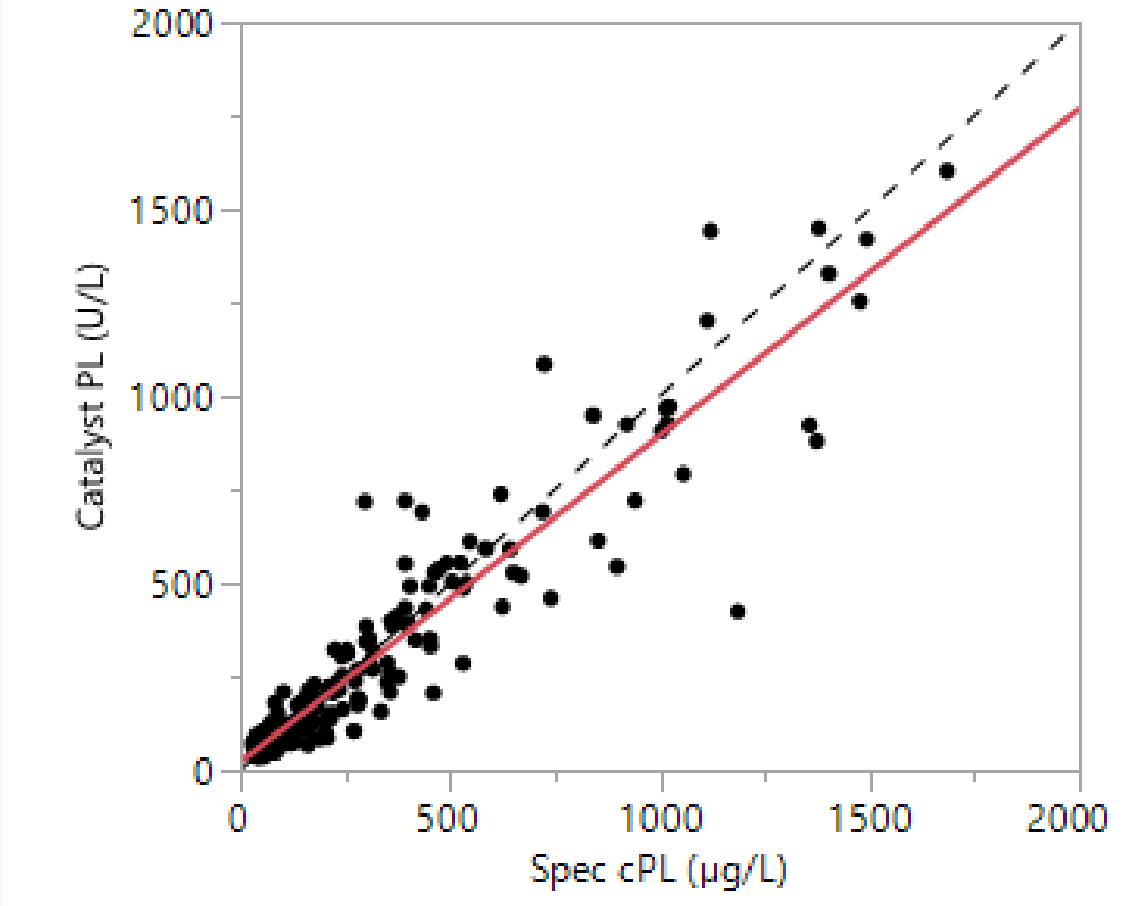


1,2-diglyceride

15 samples > 450 U/L

Lower 25% of RI
Limit of Quantification

Method Comparison



Serum lipase activity - summary

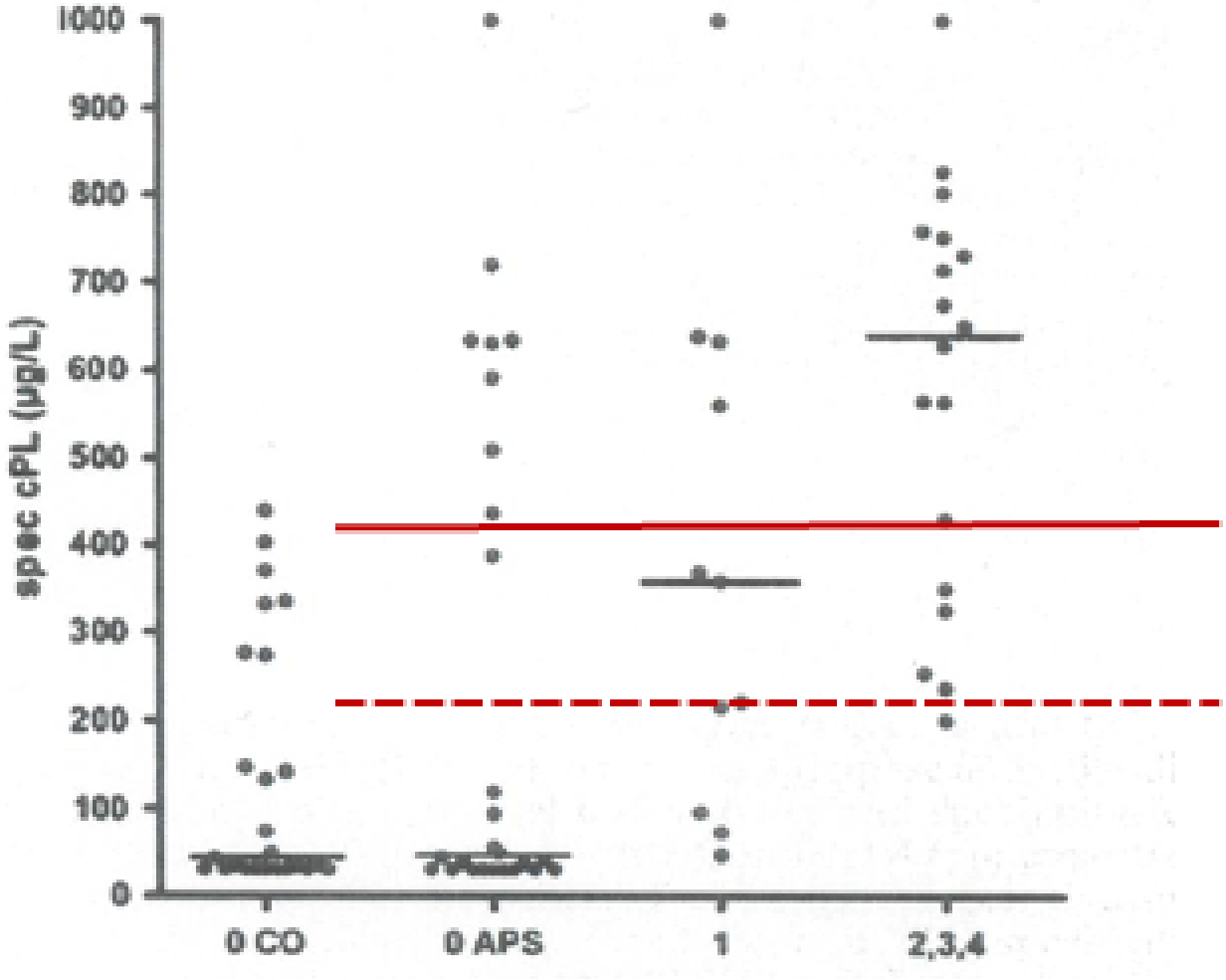
- only few assays currently available are truly specific for pancreatic lipase and thus pancreatitis
- depending on the substrate, elevated in some patients with spontaneous pancreatitis

⇨ assay must be carefully chosen based on specific data for the assay

Lipase Immunoassays

- Use an antibody that recognizes a specific moiety of the lipase molecule
- Helps avoid detection of extra-pancreatic lipases

Multicenter Study



CO = not suspected
APS = suspected
1 = not primary pancreatitis
2 = possibly pancreatitis
3 = probably pancreatitis
4 = pancreatitis

specificity: 78%
sensitivity: 93%

McCord et al. 2009

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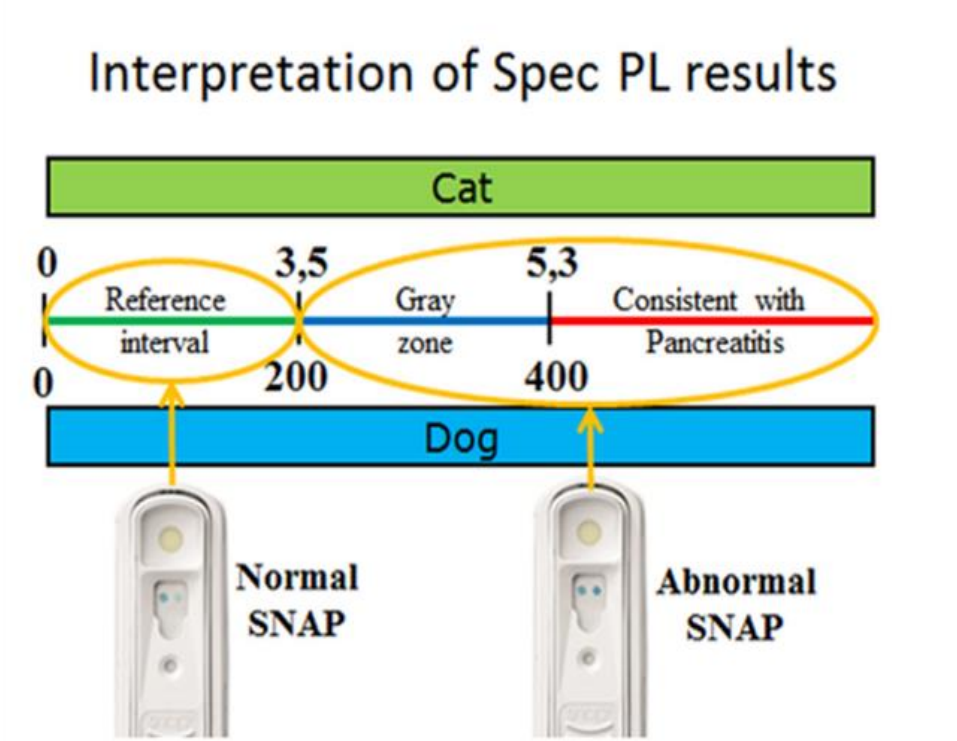
Diagnosis – immunological lipase assays

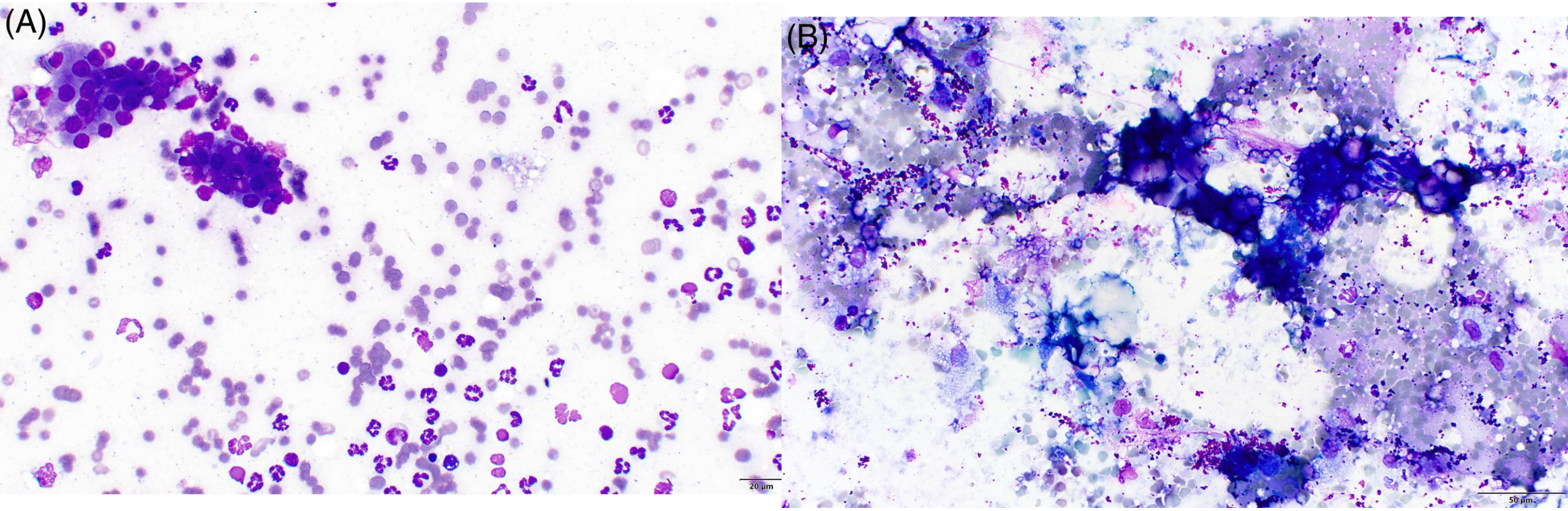
- Snap cPL
- Rapid POCT
- Semiquantitative
- Correlated well with Spec cPL assay
- *spIN **snOUT***
- Great as a **RULE-OUT** test
  - Negative rules out pancreatitis
  - Positive suggests pancreatitis – should get a Spec cPL to confirm diagnosis & act as a baseline for monitoring.



Xenoulis, P. G. and J. M. Steiner. (2016). SNAP Tests for Pancreatitis in Dogs and Cats: SNAP Canine Pancreatic Lipase and SNAP Feline Pancreatic Lipase. Topics in Companion Animal Medicine 31: 134-139.

Pancreatic Cytology

- Fine-needle aspiration is very safe in dogs
- Very useful to confirm an inflammatory process (high specificity)
- Less useful to rule out an inflammatory process (low sensitivity) – multi focal disease



Cridge et al. 2021

Management Components

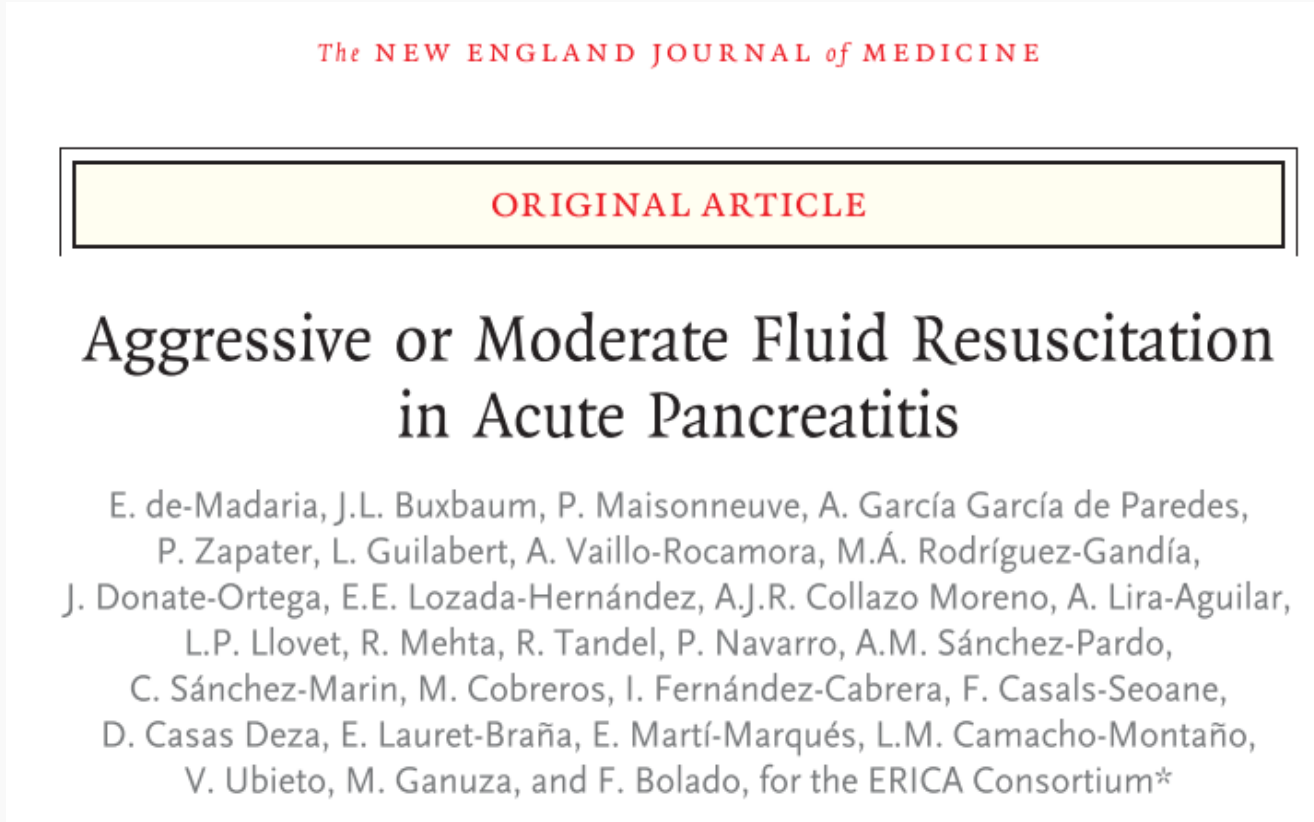
- Treatment of cause/risk factors
- Supportive & symptomatic care
- Novel therapeutics

Treatment of Cause

- Treatment of any identified risk factors:
  - Hypercalcemia, hypertriglyceridemia, others
  - Treatment of hypovolemia
  - Limit exposure to unnecessary drugs
    - especially those that have been shown to cause pancreatitis in any species
    - is the drug needed?
    - is there another alternative?

Fluid therapy – moderate vs aggressive?

- Dehydration common in AP
- Susceptible to microcirculatory changes
- WATERFALL study in people
  - Moderate VS aggressive
  - No difference in preventing progression moderate-severe AP
  - Reduces incidences of fluid overload



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis

E. de-Madaria, J.L. Buxbaum, P. Maisonneuve, A. García García de Paredes, P. Zapater, L. Guilabert, A. Vaillo-Rocamora, M.Á. Rodríguez-Gandía, J. Donate-Ortega, E.E. Lozada-Hernández, A.J.R. Collazo Moreno, A. Lira-Aguilar, L.P. Llovet, R. Mehta, R. Tandel, P. Navarro, A.M. Sánchez-Pardo, C. Sánchez-Marin, M. Cobreros, I. Fernández-Cabrera, F. Casals-Seoane, D. Casas Deza, E. Lauret-Braña, E. Martí-Marqués, L.M. Camacho-Montaño, V. Ubieto, M. Ganuza, and F. Bolado, for the ERICA Consortium*

- ***Aggressive: 20 ml/kg bolus, followed by 3 ml/kg/hour***
- ***Moderate: 10 ml/kg bolus, followed by 1.5 ml/kg/hour***

However…

- while overhydration must be avoided, appropriate fluid management must also be provided
  - replacement of lost fluids (dehydration compensation)
  - replacement of ongoing losses
  - maintenance fluids
- fluid needs must be re-estimated every few hours

Nutritional Considerations

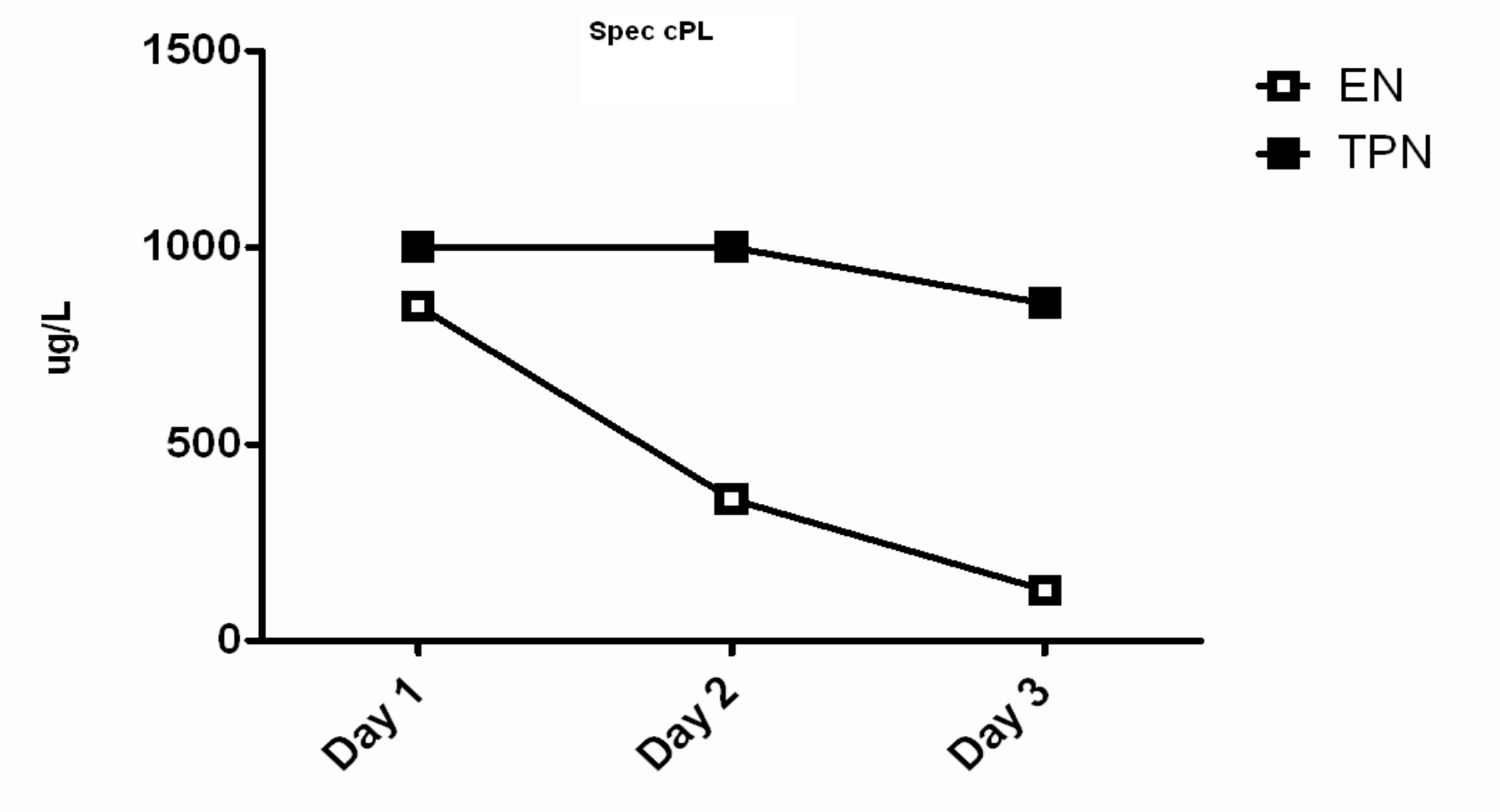
- Acute pancreatitis is a highly catabolic disease
- Routine NPO is no longer suggested for patients with acute pancreatitis
- Outcome in human patients improves if patients receive caloric support
- Relevant questions:
  - enteral vs. parenteral?
  - prepancreatic vs. postpancreatic?

Comparison of Enteral and Parenteral Nutrition in Dogs

- 10 dogs
  - 5 fed parenterally
  - 5 fed by esophagostomy tube
- There was no difference in mortality
- Disease severity score decreased more rapidly in dogs fed by esophagostomy tube

Mansfield et al. 2009

Comparison of Enteral and Parenteral Nutrition in Dogs



Mansfield et al. 2009

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Nutritional Support

- Enteral nutrition is suggested over parenteral nutrition
- Pre-pancreatic nutrition is suggested for most patients
- Gastrostomy and nasogastric tubes can be used in patients that can not be fed by the enteral route, partial or total parenteral nutrition can be employed

Nutrition – low fat?

People

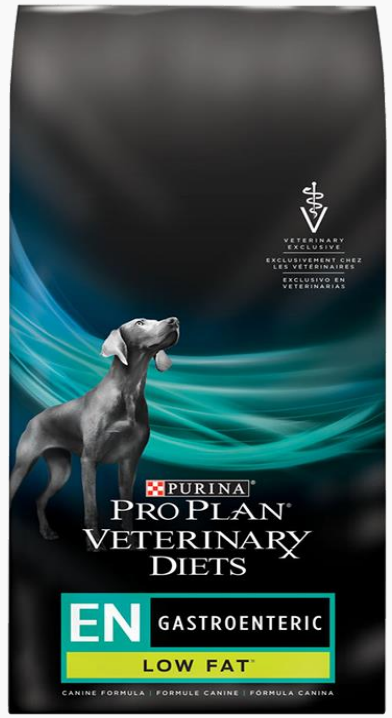
- hypertriglyceridemia
  - 3rd leading cause of AP
  - worse prognosis
- low-fat diet recommended
- tight regulation of triglyceride (<266 mg/dL) in hospital

Dogs

- low-fat highly digestible diet recommended (20 g/1000 kCal of fat)
- no definitive evidence that low-fat diet is essential
- what level is adequately low?
- after discharge:
  - manage hypertriglyceridemia with diet, underlying disease, other drugs (omega acid, fibrates)

Current Dietary Recommendations

- low-fat diet (< 20 g fat/1000 kcal)
- only low-fat treats:
  - vegetables
  - fruits
  - low-fat treats
  - home-made treats

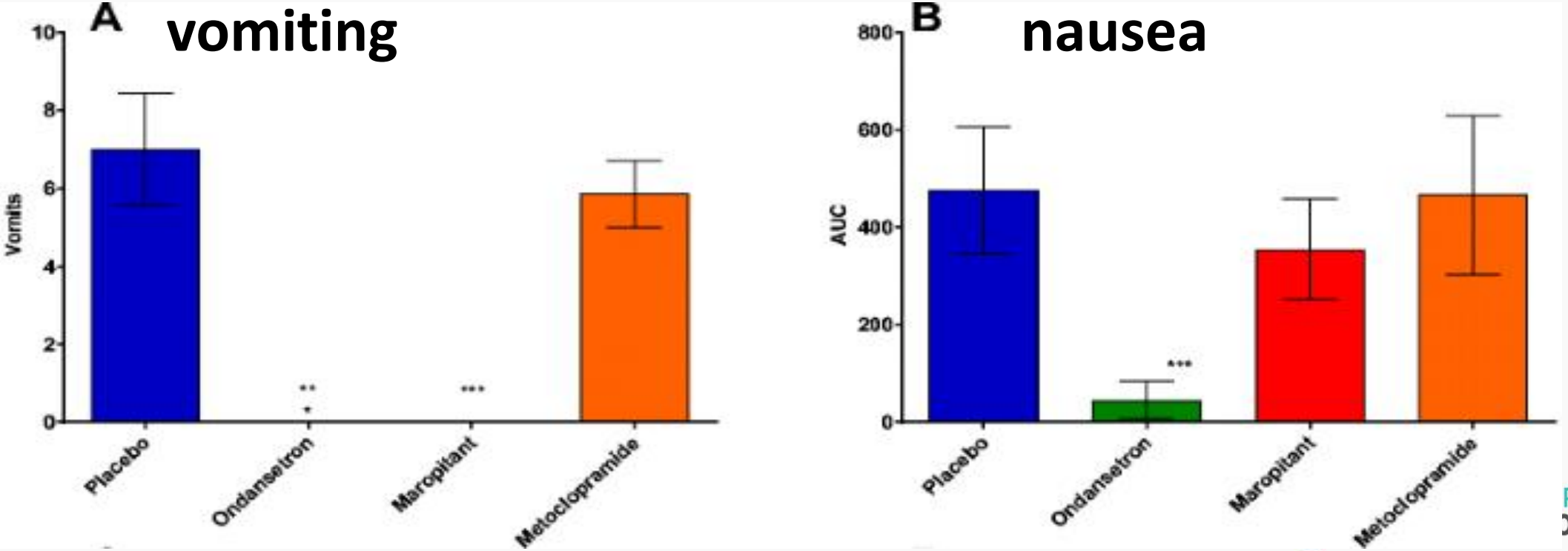


Liquid Diet

- Good choice for small tubes (NG/NE)
- 0.9 – 1.0 kcal/ml
- Approximately 20% of calories as fat
- Or 1.9 g of fat/100 kcal

Anti-emetics and anti-nausea

- ondansetron or other 5-HT_3 antagonists
- maropitant - NK_1 antagonist



Anti-emetics and anti-nausea

- metoclopramide – D2 antagonist centrally, mild 5-HT3 antagonist peripherally)
  - weak anti-emetic
  - more useful as a prokinetic
  - dopamine receptors are involved in the modulation of pancreatic perfusion and in the anti-inflammatory cascade in AP

  → potentially counterproductive

Analgesia

- 33 – 77% of dogs with AP have abdominal pain
- Opioids
  - Full μ agonists for severe pain
  - Partial μ agonists for milder pain
  - Avoid butorphanol – no analgesic effect
  - Do not mix different groups of opioids
- Typically, full μ → partial μ
- Multimodal approach “FLK” protocol
- Outpatient – fentanyl patch, Zorbium®
- AVOID NSAIDS

Side-effects

- Functional ileus
- Obtundation →risk of aspiration
- Nausea
- respiratory compromise

Complications

- Severe forms of pancreatitis can be associated with a multitude of systemic complications:
  - electrolyte and acid/base imbalances
  - disseminated intravascular coagulation
  - myocarditis
  - acute renal failure
  - pulmonary failure
  - multiorgan failure

⇨ careful monitoring and early intervention are key to successful recovery

Other Management Strategies

- Antibiotics?

Antibiotics in Patients with Acute Pancreatitis

- Infectious complication may be a late cause of death in humans with pancreatitis
- Several meta-analysis studies did not find a beneficial effect of antibiotics in these patients
- Recent treatment recommendations do not include routine use of antibiotics
- Never been systematically studied in dogs
- Dogs with severe acute pancreatitis usually do not reach the late stage of the disease

Other Management Strategies

- anti-inflammatory agents?

Anti-Inflammatory Agents - Steroids

- Steroids are not considered to be useful for the routine treatment of humans with acute pancreatitis
- A Japanese study suggested a beneficial effect in dogs with acute pancreatitis - retrospective
- Corticosteroids have a wide variety of effects

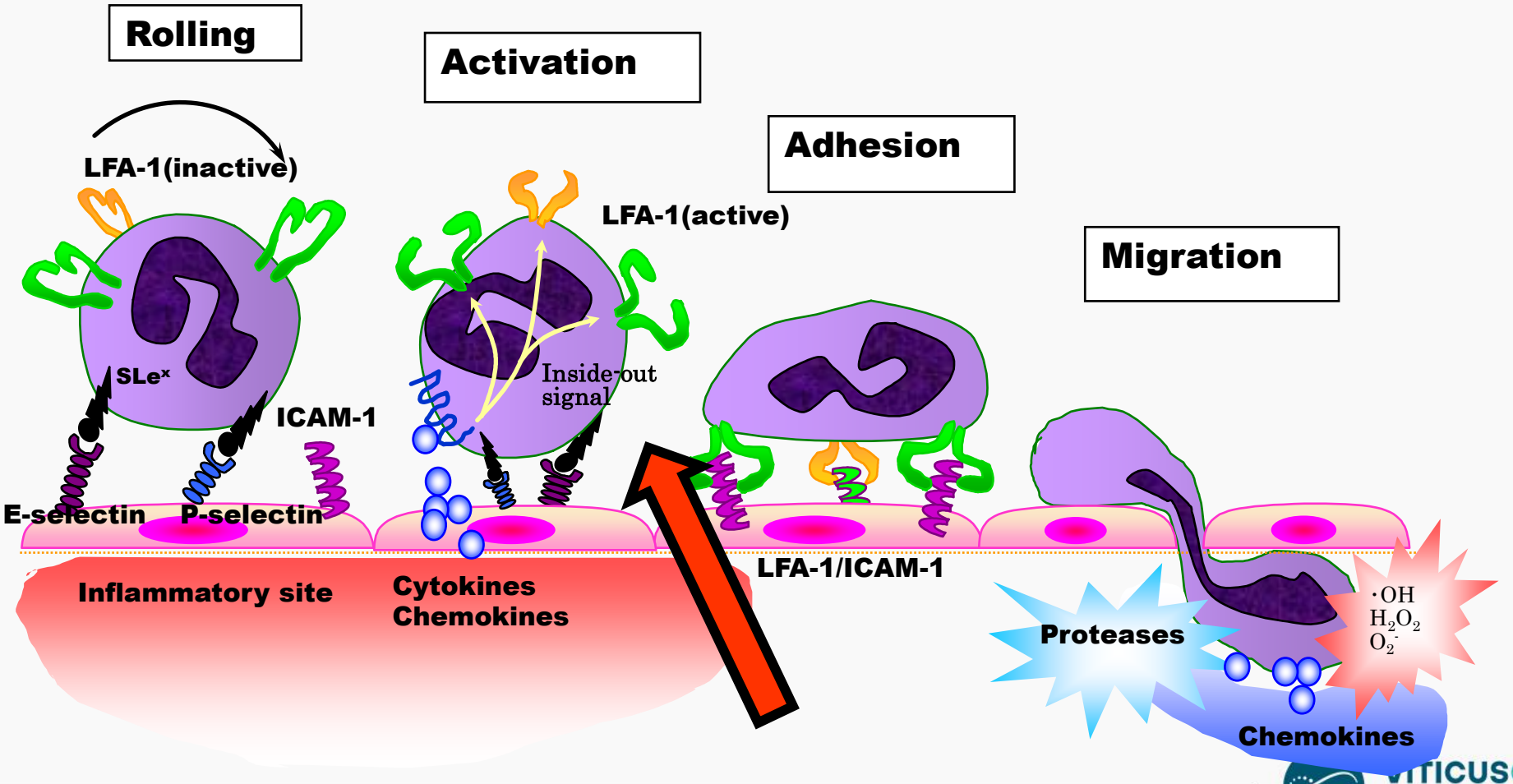
Fuzapladib Sodium

- Fuzapladib has recently received conditional approval by the FDA
- PANOQUELL®-CA1 (fuzapladib sodium for injection)

Fuzapladib Sodium

- A novel drug that acts as a leukocyte (lymphocyte) function-associated antigen-1 (LFA-1) activation inhibitor
- Proof of concept shown in canine experimental pancreatitis
- Clinical efficacy demonstrated in a controlled clinical trial in Japan
- Controlled multi-center clinical trial in the USA demonstrated positive effects

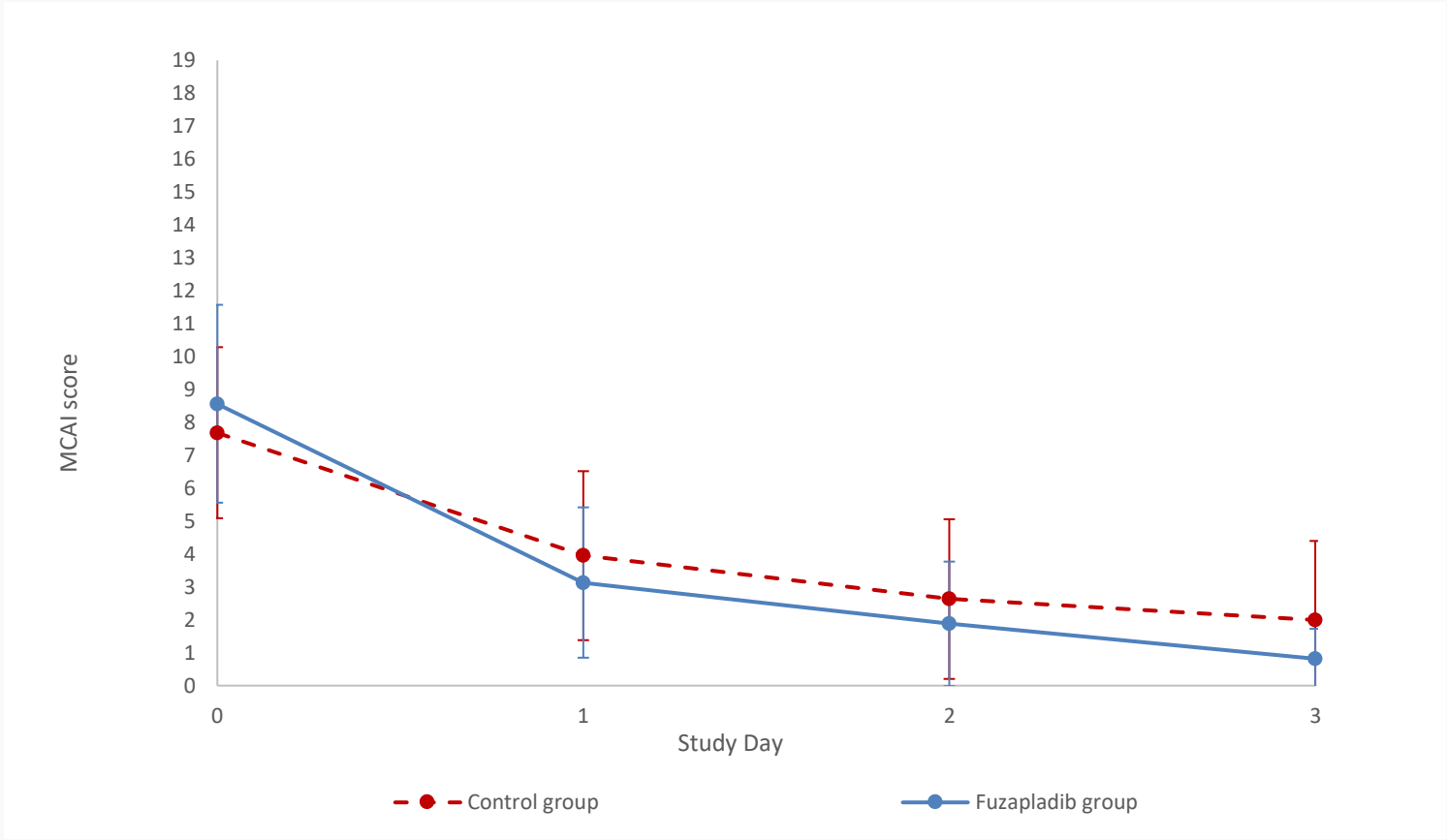
Mode of Action



US multi-center controlled clinical trial

- 35 dogs
  - treatment group: 16
    - fuzapladib 0.4 mg/kg q 24 hrs IV for 3 days
  - control group: 19
    - placebo (not noticeably different from treatment)

MCAI



MCAI

- Activity
- Appetite
- Vomiting
- Abdominal pain
- Dehydration
- Fecal consistency
- Blood in the stool

Take Home Points

❶ Pancreatitis is more common than previously believed

❷ The optimal diagnosis is achieved by integrating all clinical data, including history, imaging, and clinical pathology

❸ A new DGGR-based lipase assay for the Catalyst is available that is specific for the measurement of pancreatic lipase and thus a diagnosis of pancreatitis

Take Home Points

❹ Until recently the standard of care was centered on supportive and symptomatic care

❺ Fuzapladib sodium offers a novel treatment strategy for dogs with pancreatitis and has received conditional approval by the FDA

Questions?


GASTROINTESTINAL LABORATORY
G I
TEXAS A&M UNIVERSITY


COLLEGE OF VETERINARY MEDICINE