LOVE IT OR LIVER

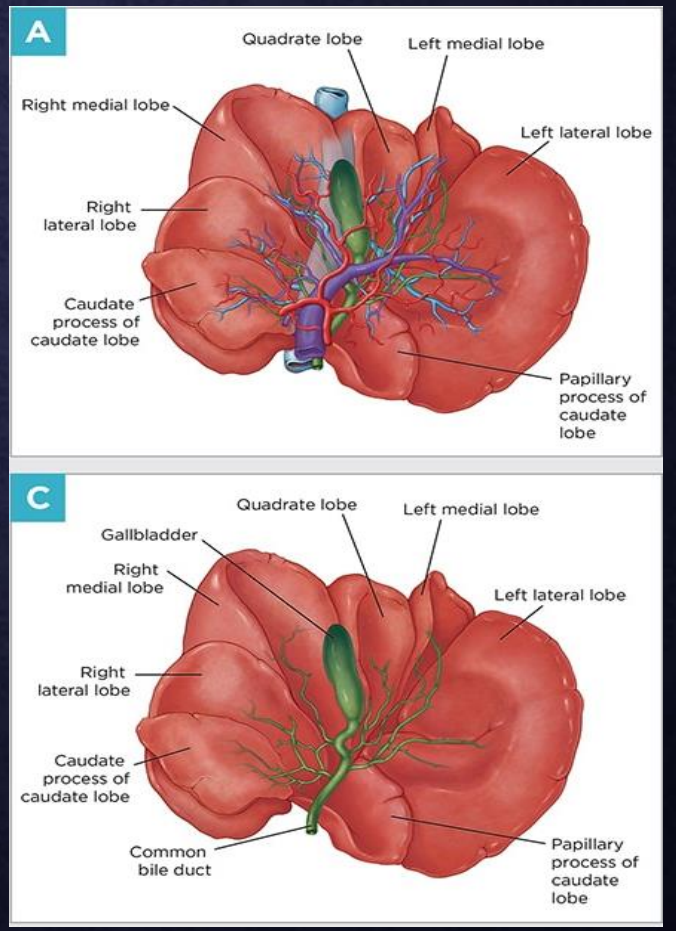
CANINE LIVER ENZYME ELEVATION… NOW WHAT?

NEDRA WILSON, BVETMED, DACVR
SALLY PURCELL, DVM, DACVIM

DIAGNOSTIC IMAGING

LIVER ANATOMY & PHYSIOLOGY

- Most important vital organ
- Largest gland
- Large reserve capacity
- Regeneration
- So many functions
  - Metabolism
    - Fat, CHO, protein, drugs, hormones
  - Production/excretion of bile
  - Protein synthesis
  - Detoxification
  - Storage
    - Iron, B12, folic acid

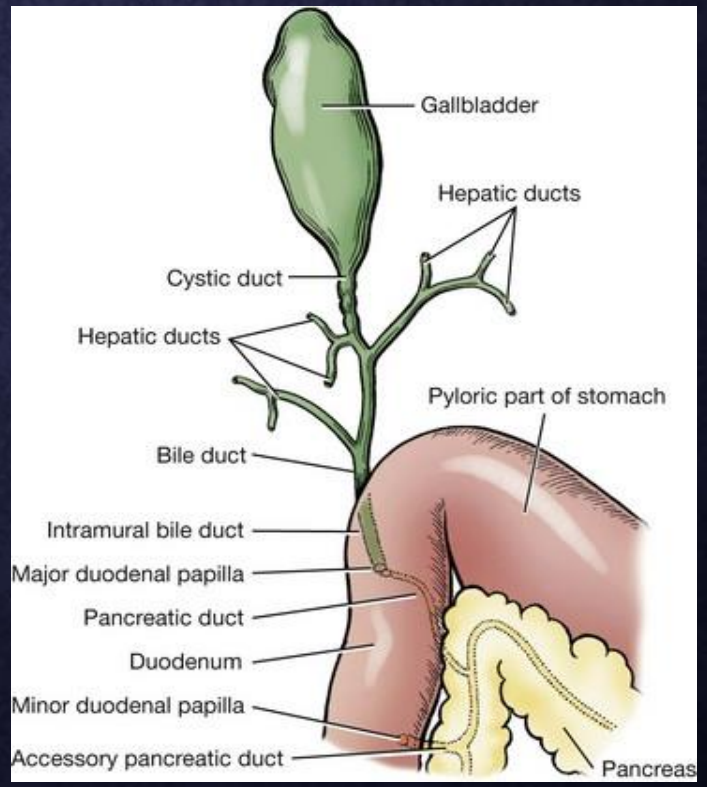


GALLBLADDER ANATOMY & PHYSIOLOGY

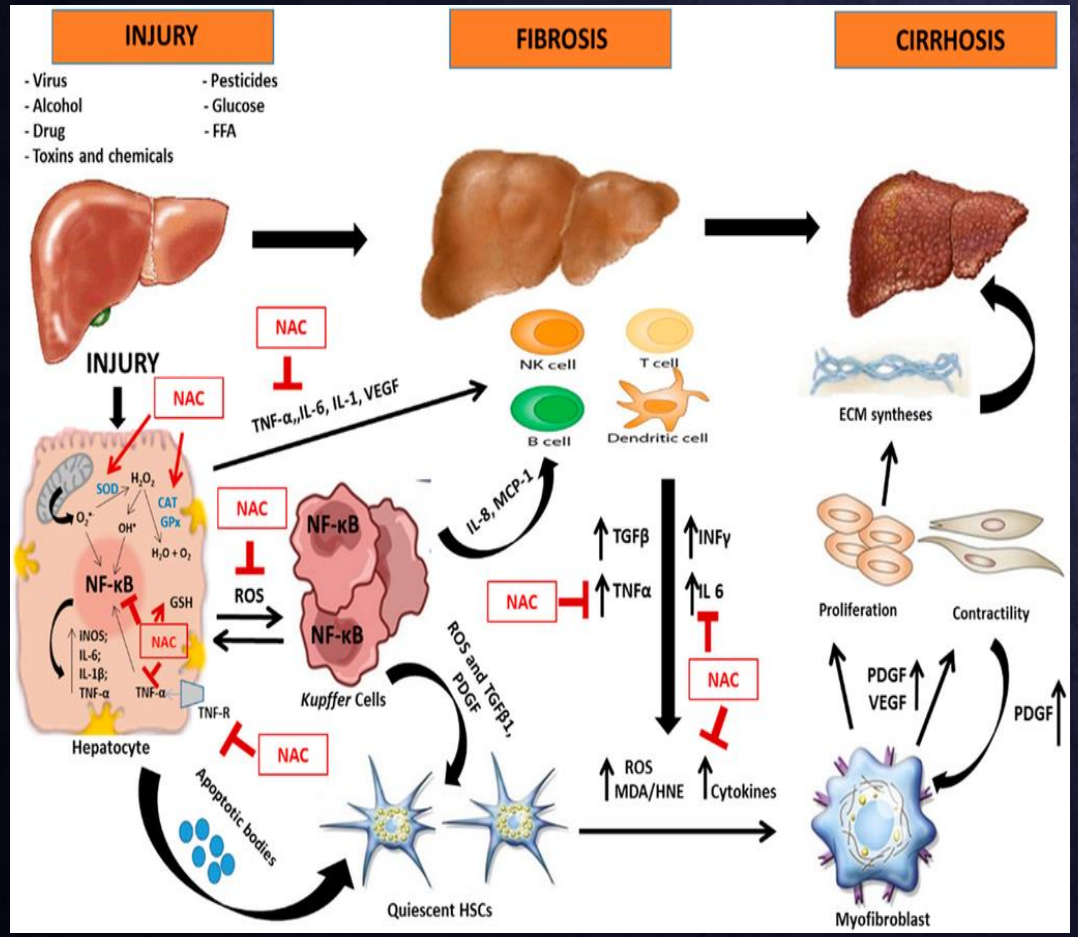
- Bile storage & concentration
- Release of bile into duodenum

Bile

- Neutralize stomach acid
- Antifungal, antibiotic properties
- Digestion/absorption of dietary fats
- Absorb fat soluble vitamins



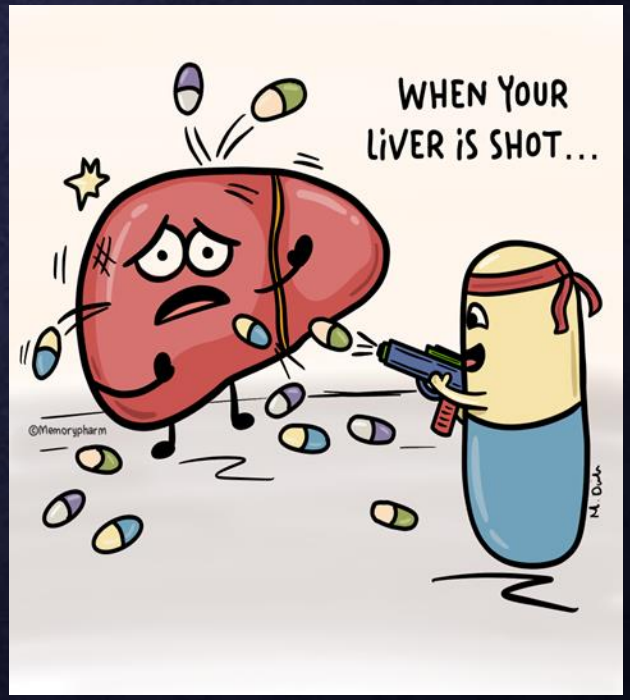
MECHANISMS OF LIVER INJURY



- Oxidative Injury
  - Present in most forms of hepatopathy
  - Ultimately leads to fibrosis
- Toxins, endotoxins, and infectious agents
  - Sentinel position between splanchnic and systemic circulation
  - Obstructive cholestasis and hepatobiliary inflammation
- Cholestatic liver disease
  - Impaired bile flow is damaging to the tissues
  - Leads to inflammation, oxidative damage, and retention of toxins

MECHANISMS OF LIVER INJURY

- Immune-mediated mechanisms
  - Augments injury initiated by other mechanisms
  - Not well understood
    - Molecular mimicry
    - Innocent bystander effect
- Copper and iron
  - Necessary to catalyze important reactions
  - Iron – accumulates in macrophages
  - Copper
    - Genetic transport or storage disorder – rare
    - Secondary to cholestasis – most common



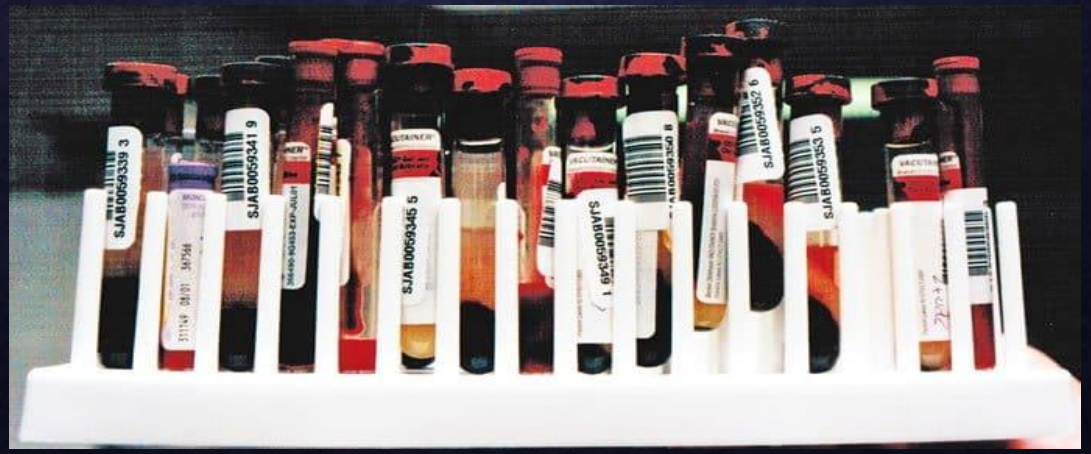
DIAGNOSTIC CONSTRAINTS OF LIVER DISEASE

- Definitive diagnosis is ideal providing the best opportunity for treatment success.
- Reality
  - Identification of initiating factor or diagnosis is not always possible
    - Financial concerns
    - Ambiguous diagnostic test results
- Clinical signs often do not appear until the disease is fairly advanced
- There is no ideal liver function test that will establish the extent of liver damage.

BIOCHEMICAL TESTS

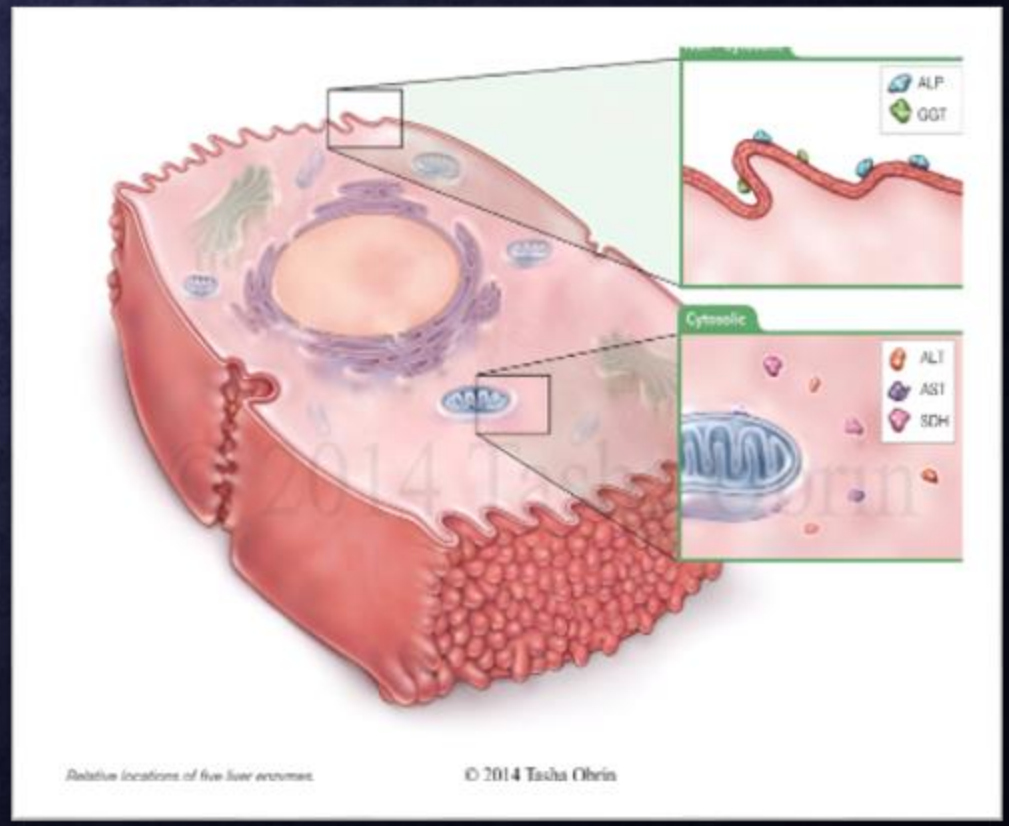
Three Big Categories

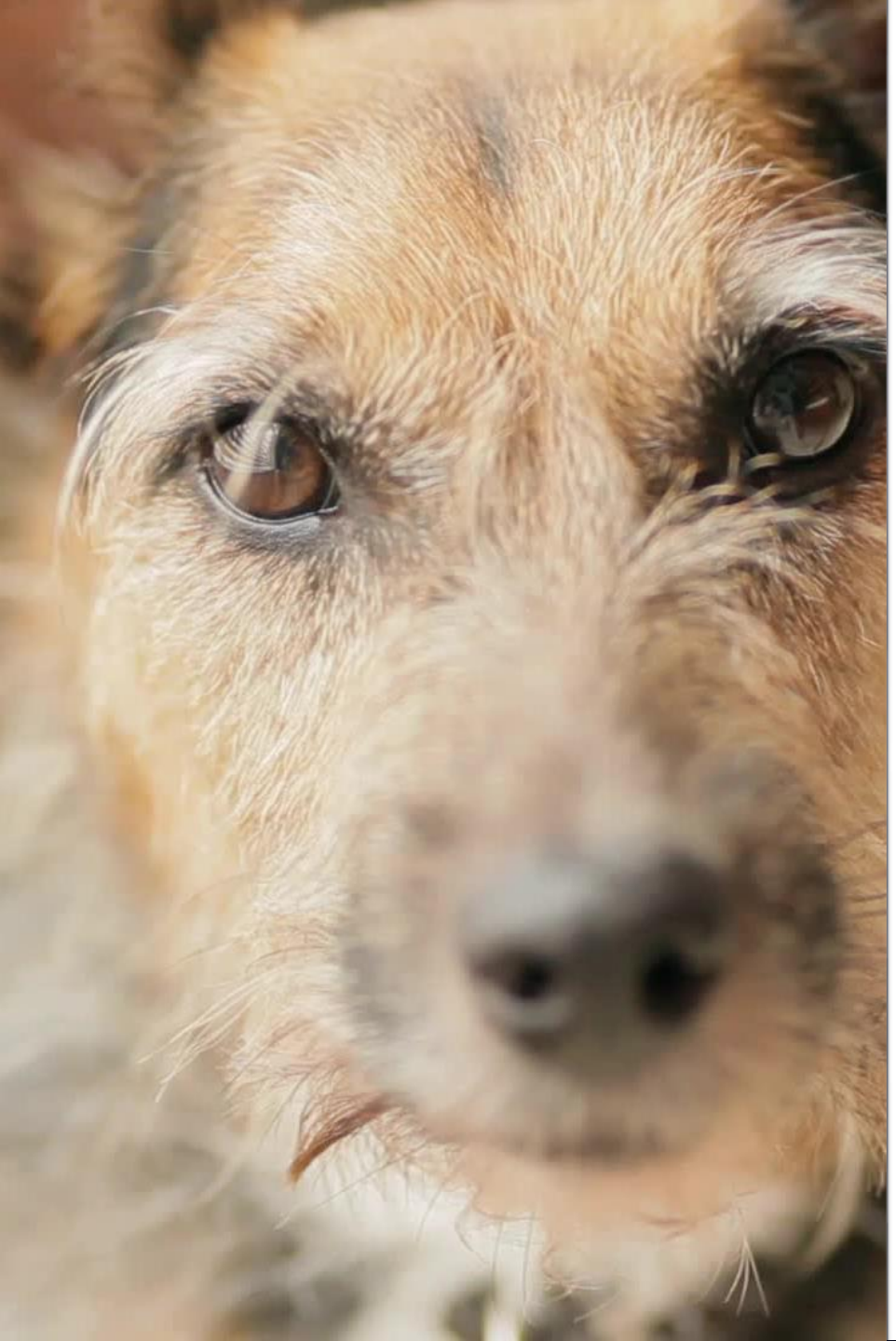
- Tests of hepatocellular injury (aka leakage)
- Cholestatic markers
- Tests of impaired metabolic function or synthetic capacity



ALANINE TRANSFERASE (ALT)

- ALT is located in the cytoplasm
  - Liver, muscle, rbcs
- Half life is 2.5-3 days.
- HOWEVER practically it takes 1-2 weeks to normalize
- Leakage from damaged hepatobiliary cells
- Elution from damaged membranes
- Increased synthesis





ELEVATED ALT

- Fairly common finding
  - 20% of sick dogs presented to referral practice
  - 47% of both sick and healthy dogs presented to GP
- 80-100% sensitivity
  - Inflammation, necrosis, vacuolar hepatopathy, primary neoplasia
- 50-80% sensitivity
  - Congestion, metastasis, portosystemic shunt

HEPATOBILIARY CAUSES

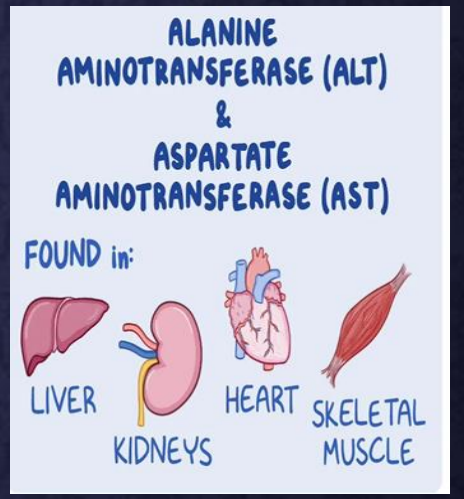
- Chronic hepatitis/cirrhosis
  - Labrador, spaniels, Doberman, Dalmatian
- Copper-associated hepatopathy
  - Bedlington terrier, Westie, Dalmatian, Doberman, Labrador
- Nodular hyperplasia
- Primary neoplasia
- Vacuolar hepatopathy
- Infectious/hepatic abscess
- Inflammatory
- Toxin
- Hepatocutaneous syndrome
- Liver lobe torsion
- PSS/MVD(PH)

NON-HEPATOBILIARY CAUSES

- Endocrine
  - DM, Cushing's
- GI disease
  - Pancreatitis
  - IBD
- Metastatic neoplasia
- Hypoxia/hypotension
  - CHF
  - Hypotensive crisis
  - Severe hemolytic anemia
  - Status epilepticus
- Systemic infections
- Abdominal trauma
- Drug induction
  - Phenobarbital
  - Steroids
  - CBD

ASPARTATE AMINOTRANSFERASE (AST)

- In the cytoplasm of liver cells
- Non-hepatic sources
  - Muscles
  - Cardiac tissues
  - Kidneys
- Half-life is 12-24 hrs
- If from liver disease, it is proportional to ALT elevation
- In case of disproportional increase, measure CK
- AST is more sensitive than ALT for metastatic liver diseases

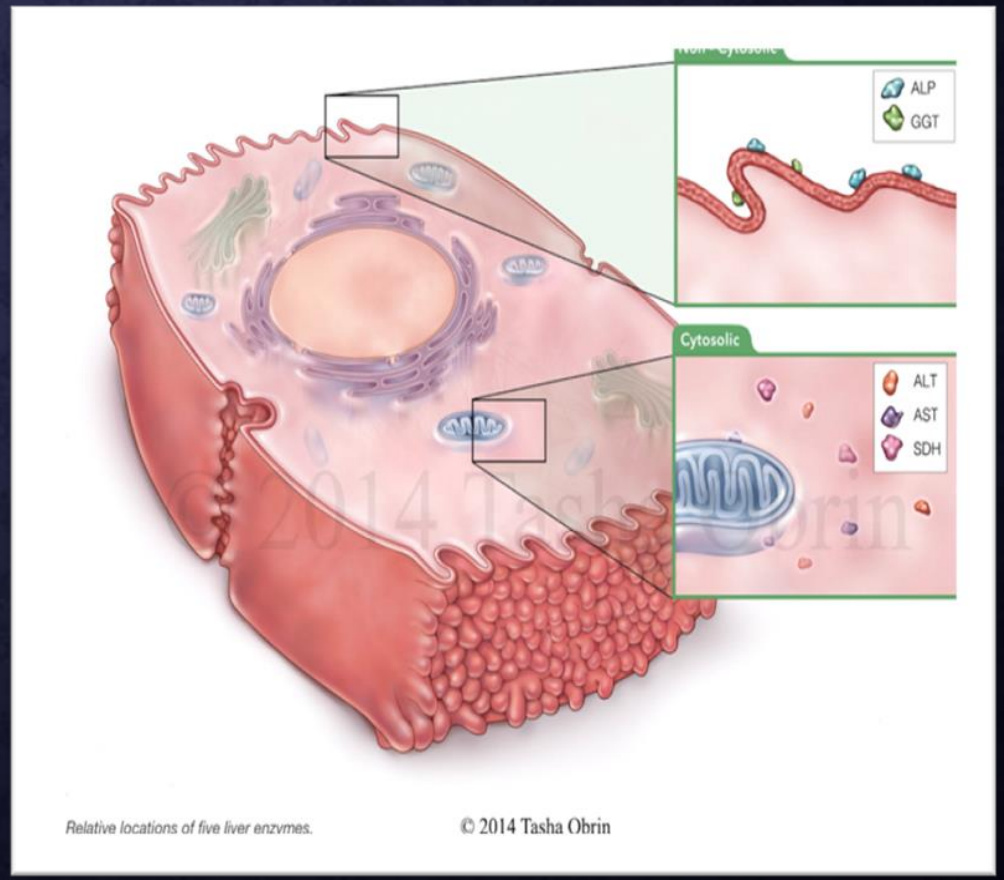


HOW HIGH IS TOO HIGH?

- Degree of increase does not correspond with degree of illness
  - Makes it more likely?
  - Corelates with prognosis?
- Elevation >3-4 x upper limit of normal
- Persistent/progressive increase, >12 weeks
- Elevation along with any clinical evidence of liver dysfunction
- Any increase in breeds with increased prevalence of primary hepatopathy

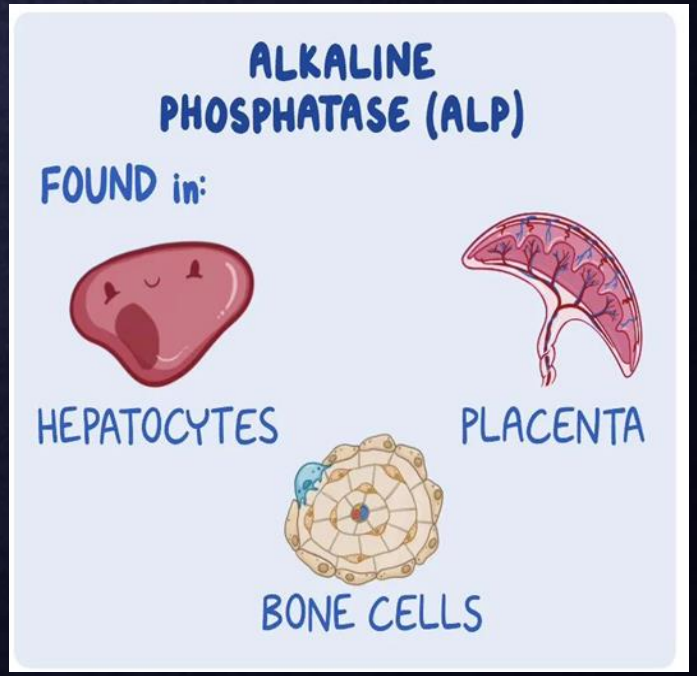
ALKALINE PHOSPHATASE (ALKP)

- VERY common lab finding
  - 39% of ALL dogs
  - 51% of dogs > 8 yrs old
- Often a diagnostic dilemma
- For liver disease
    - High sensitivity - 86%
    - Low specificity - 49%



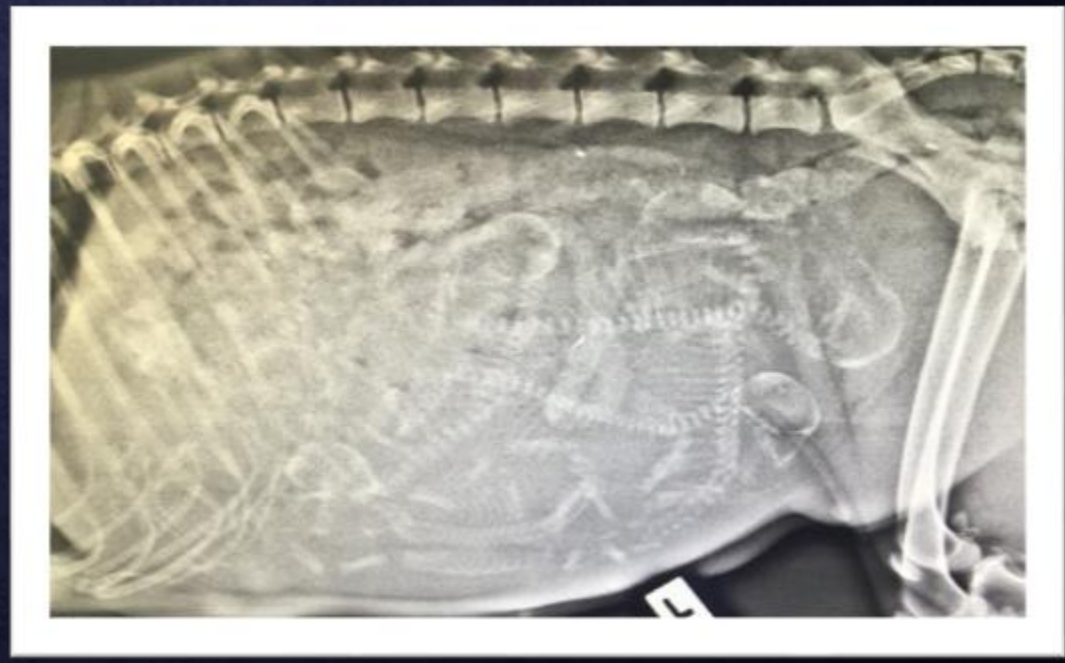
ALKALINE PHOSPHATASE (ALKP)

- Heterogeneous group of enzymes
  - Catalyze the hydrolysis of phosphate alkaline pH
  - Poorly defined biologic functions
    - Studied for decades
    - Still don’t know
- Total serum ALKP
  - L-ALP - liver
  - B-ALP - bone
  - C-ALP - corticosteroid (dog only)
  - Other



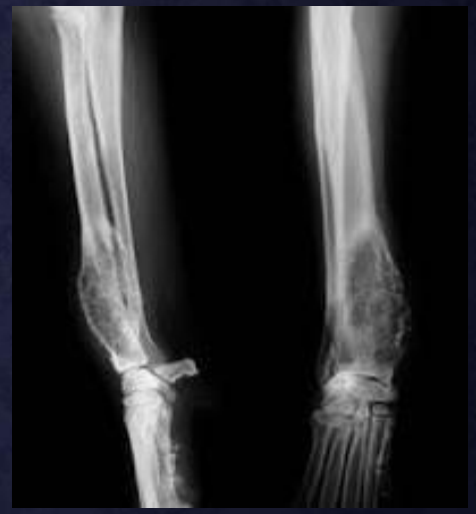
BONE ALKALINE PHOSPHATASE

- Attached to the external cellular membrane of osteoblasts
- Function is unknown???
- Typically young, growing dogs
  - In 96% of <u>total</u> ALKP in patients <1 yr
  - Only 25% of <u>total</u> ALKP in patients >8 yr



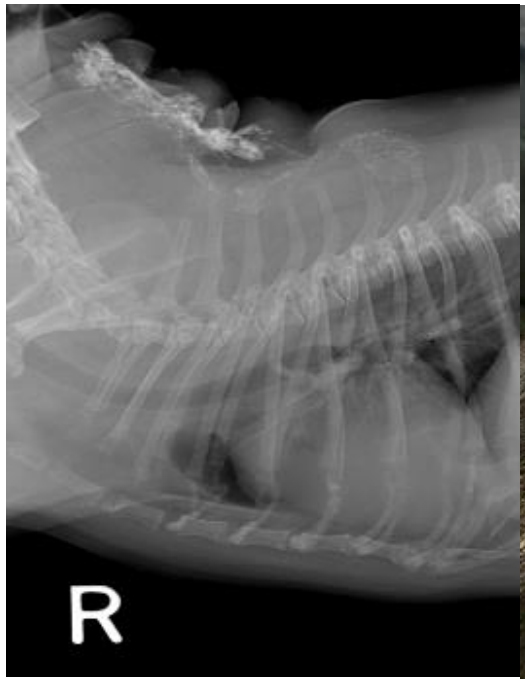
CAUSES OF INCREASED B-ALP

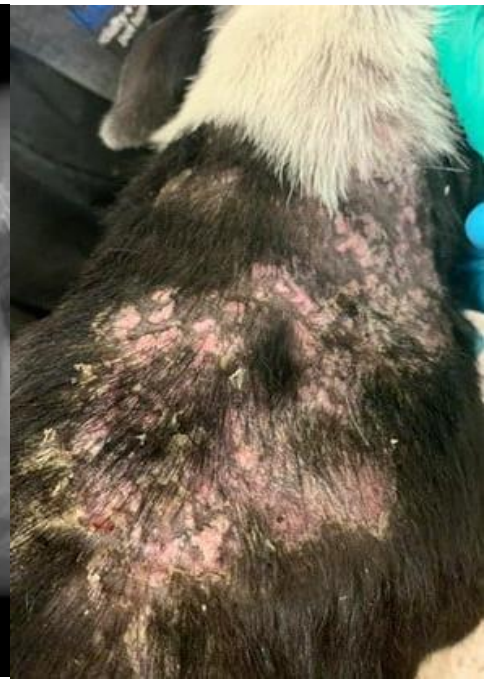
- Osteosarcoma
  - Typically, <4x ULN
  - Prognostic
- Fracture healing
- Renal 2nd hyperparathyroidism,
- Benign familial hyperphosphatemia
  - Siberian Husky
- Nutritional osteopathies



CORTICOSTEROID ALKALINE PHOSPHATASE

- Cushing's disease, exogenous steroids
- Dogs only!
- C-ALP 10-30% in normal dogs
  - Increases with age
- Can be measured at most labs but… what does it mean???
  - Very high sensitivity for Cushing's (95%)
  - Very poor specificity (18%)



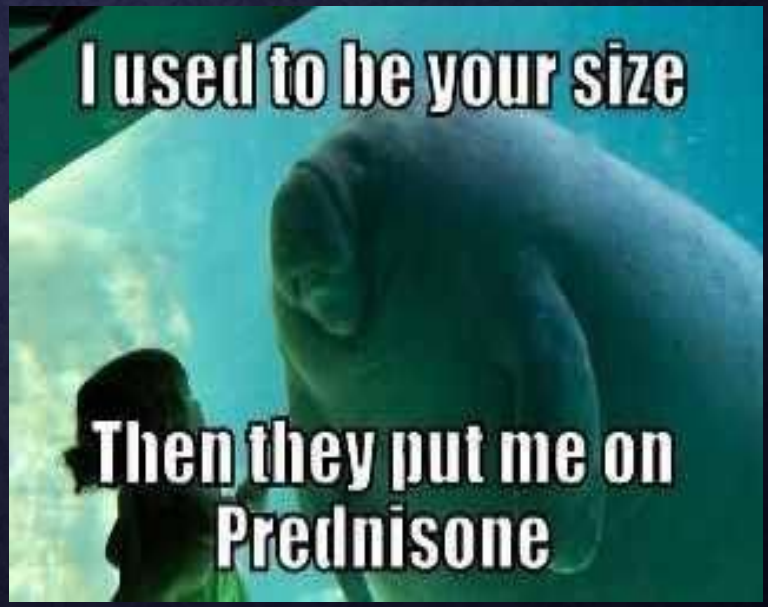


LIVER ALKALINE PHOSPHATASE

- Located predominantly in the periportal zone
  - Bile canaliculi and sinusoidal membranes
- L-ALP predominate isoenzyme in dogs >1 yr
- Two mechanisms for increase
  - Cholestasis
  - Drug induction
    - Phenobarbital
    - Exogenous steroids

COMMON CONDITIONS CAUSING ONLY ELEVATED ALKP

- Cushing's disease
- Drug induction
- Idiopathic vacuolar hepatopathy
- Hepatic neoplasia
- Nodular hyperplasia
- Breed-related



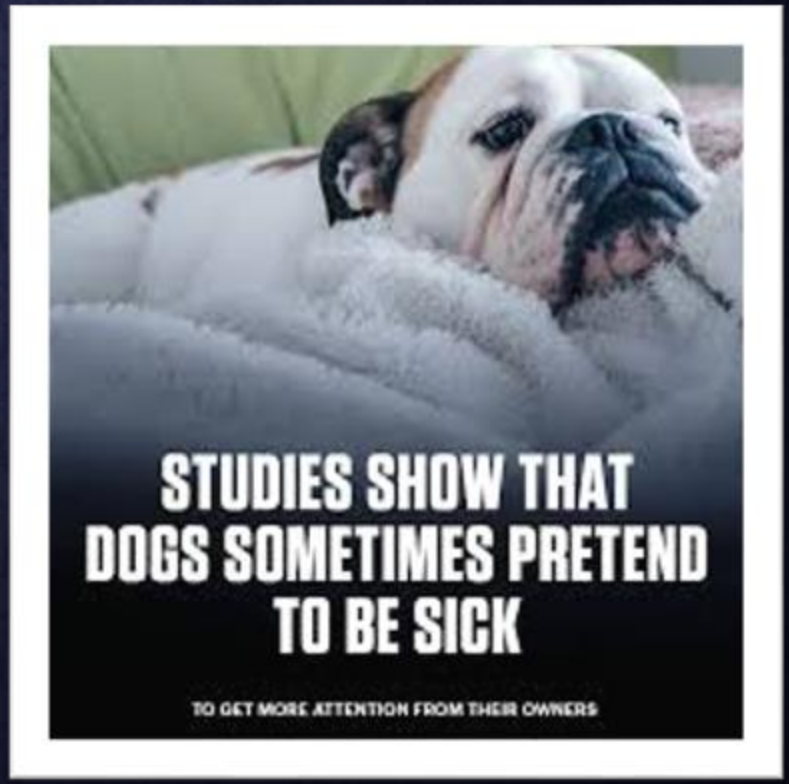
HOW HIGH IS TOO HIGH???

- Degree of increase does not correspond with degree of illness
  - Makes it more likely?
  - Corelates with prognosis?
- Dogs with ALKP associated disease
  - 1,950 +/- 1,300 U/L
- Dogs without disease
  - 970 +/- 430 U/L

(Nestor et al.)

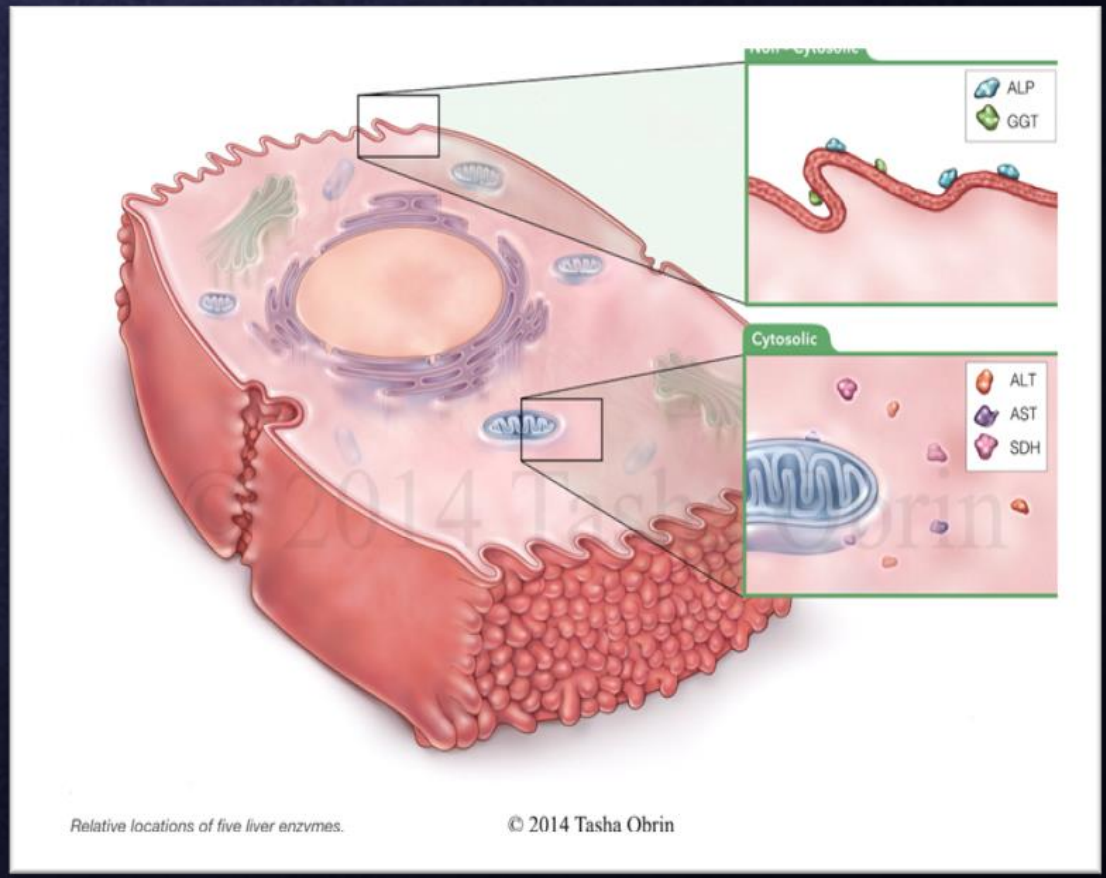
DOES HIGH ALKP CAUSE CLINICAL SIGNS?

- NO!!!
- No patient has ever died from a high ALKP
- Little to no evidence that high ALKP makes you sick
  - Enzyme does not do harm
  - Underlying disease does



GAMMAGLUTAMYL TRANSFERASE (GGT)

- Hepatocyte canalicular membrane
- GGT isoenzymes are in:
  - Hepatobiliary system
  - Kidney
  - Pancreas
  - Intestine
  - Mammary glands
- Has lower sensitivity but higher specificity for cholestatic disease than ALKP
  - Alone ALP-51%
  - Alone GGT- 80%
  - Both - > 90%

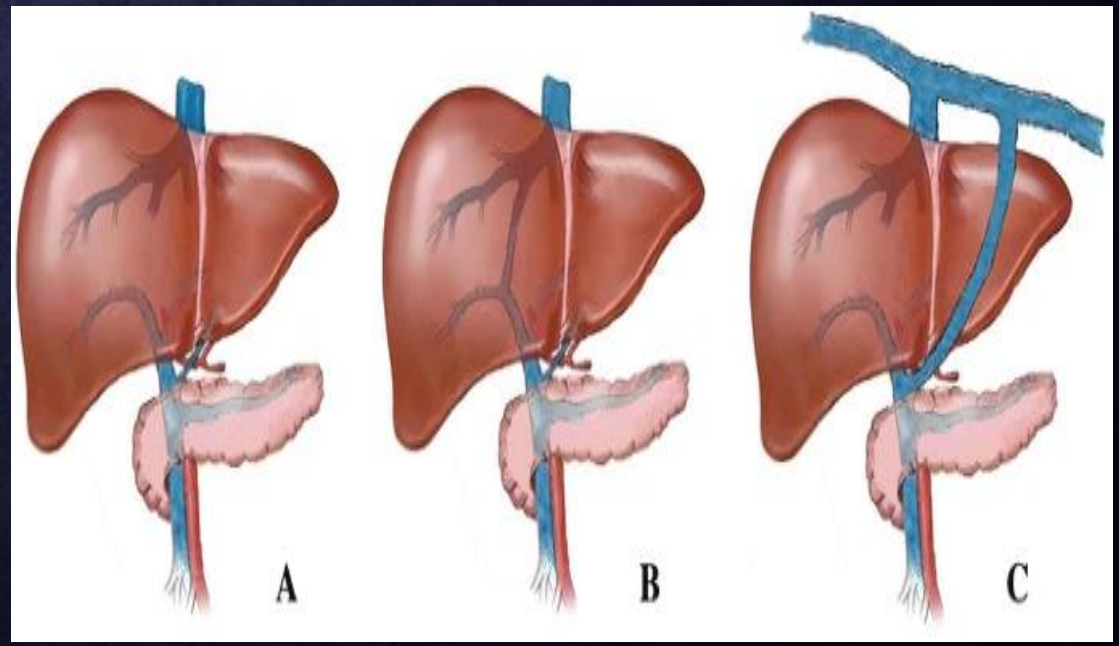


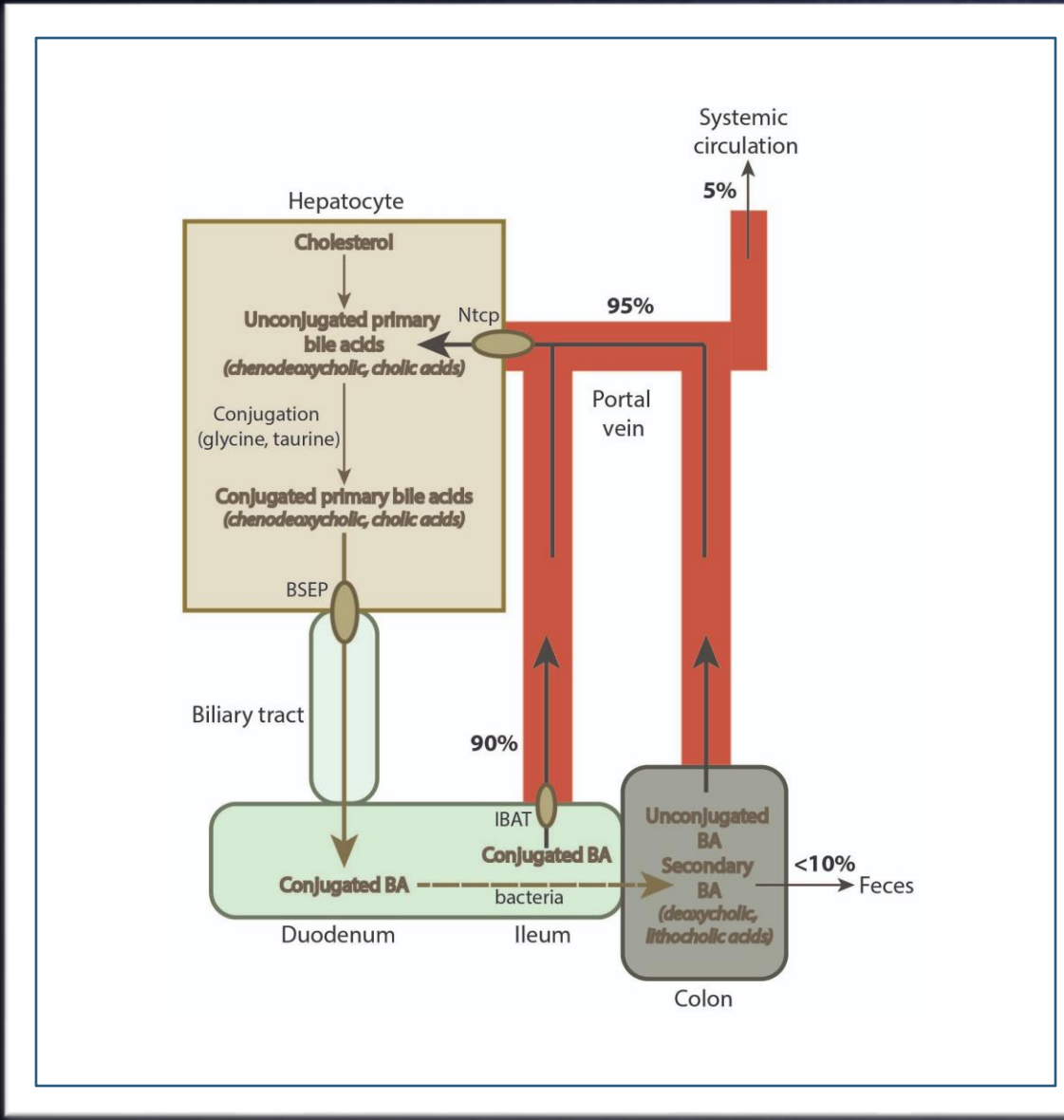
MARKERS OF LIVER FUNCTION

- Bilirubin
  - Most sensitive and specific once hemolytic disease ruled out
  - Except in sepsis
- Albumin
  - Liver >60-70% dysfunction before decreased
  - GI loss/PLE
  - Renal loss/PLN
  - Negative acute phase protein
- Urine ammonium urate/biurate crystals
- BUN
  - Chronic liver dysfunction
  - PSS
  - Low dietary protein intake
  - Starvation
- Glucose > 75% dysfunction
- Cholesterol
  - Quite variable depending on cause
  - Low-liver dysfunction
  - Elevated-cholestatic ds, endocrine ds

SERUM TOTAL BILE ACID

- Bile acid reflect efficiency and integrity of entero-hepatic circulation
- Increased bile acids can be caused by:
  - Post-hepatic icterus - bile acids leak into circulation
  - Abnormal portal circulation
    - PSS
    - MVD
  - Poor hepatic reuptake, conjugation, and re-secretion
- Bile acid cause direct toxicity when high
  - Hepatotoxicity
  - Gastric hyperacidity
  - Diarrhea





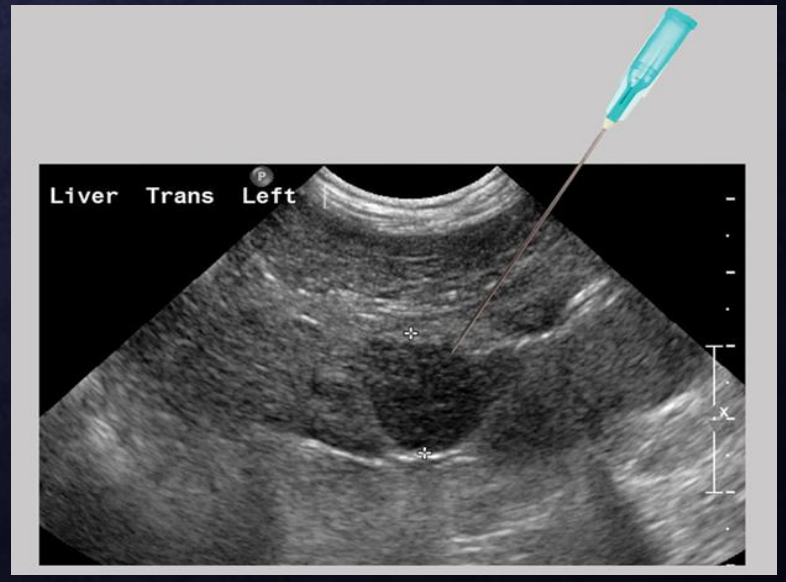
BILE ACID RECYCLING

Increased unconjugated bile acids

- Liver disease: impair the conjugation process
- Bile acid malabsorption: small intestine cannot properly reabsorb bile acids, more unconjugated bile acids may reach the colon, causing diarrhea
- Bacterial overgrowth: Excessive bacteria causes more deconjugation, increasing unconjugated forms

ADDITIONAL DIAGNOSTICS

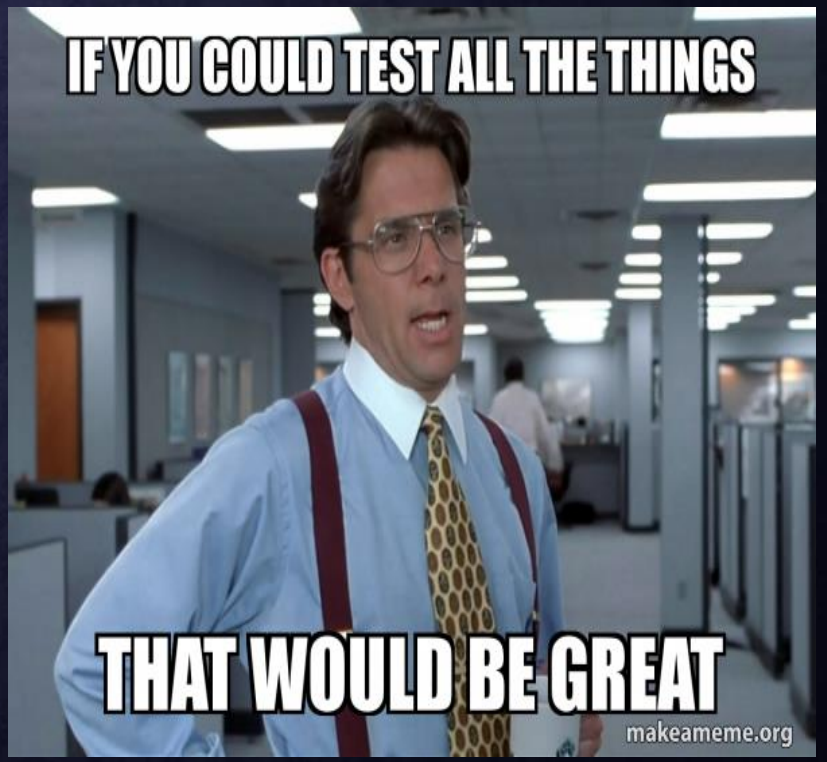
- Clotting times/fibrinogen
- Endocrine testing
  - Thyroid panel
  - Cortisol, ACTH stimulation test
  - Urine cortisol: creatinine ratio
  - LDDS
- PLI or Spec PL level
- Infectious disease testing???
- Thoracic radiographs???
- Abdominal radiographs
- Abdominal ultrasound
- Liver aspirate/biopsy



HOW TO AVOID RUNNING EVERY TEST…

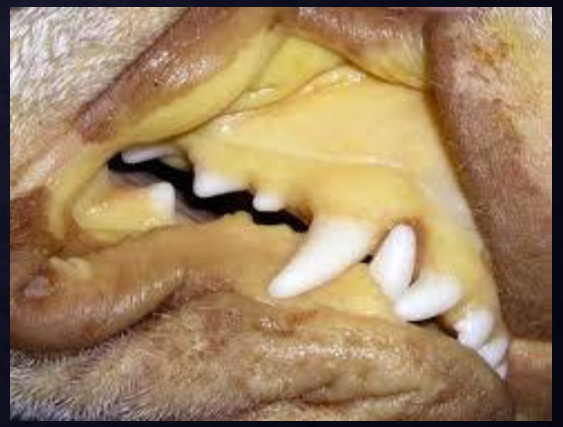
- There is no “best” order to perform diagnostic tests for all patients
- Diagnostic plans should be individualized
  - Minimize invasiveness/risk
  - Maximize owner’s financial resources

In the end…you may run every test and still not have the answer!!



MONITORING

- AST will improve first (shortest half life)
- Then ALT close behind
- Then ALKP and GGT
- Then bilirubinuria
- Then bilirubinemia (delta bilirubin due to cholestasis can take longer)
- Then jaundice will resolve (this can take days after serum bilirubin has returned to normal)
- Persistently elevated bile acids indicate persistent liver disease despite improvement of other tests



MEDICAL MANAGEMENT

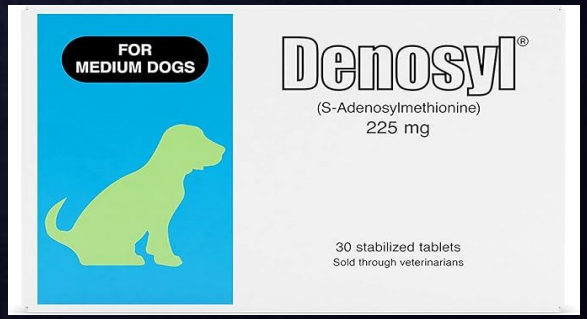
- Goals of therapy
  - Remove the etiology
  - Targeted therapy
  - General liver support
  - Adequate diet
- Multimodal approach

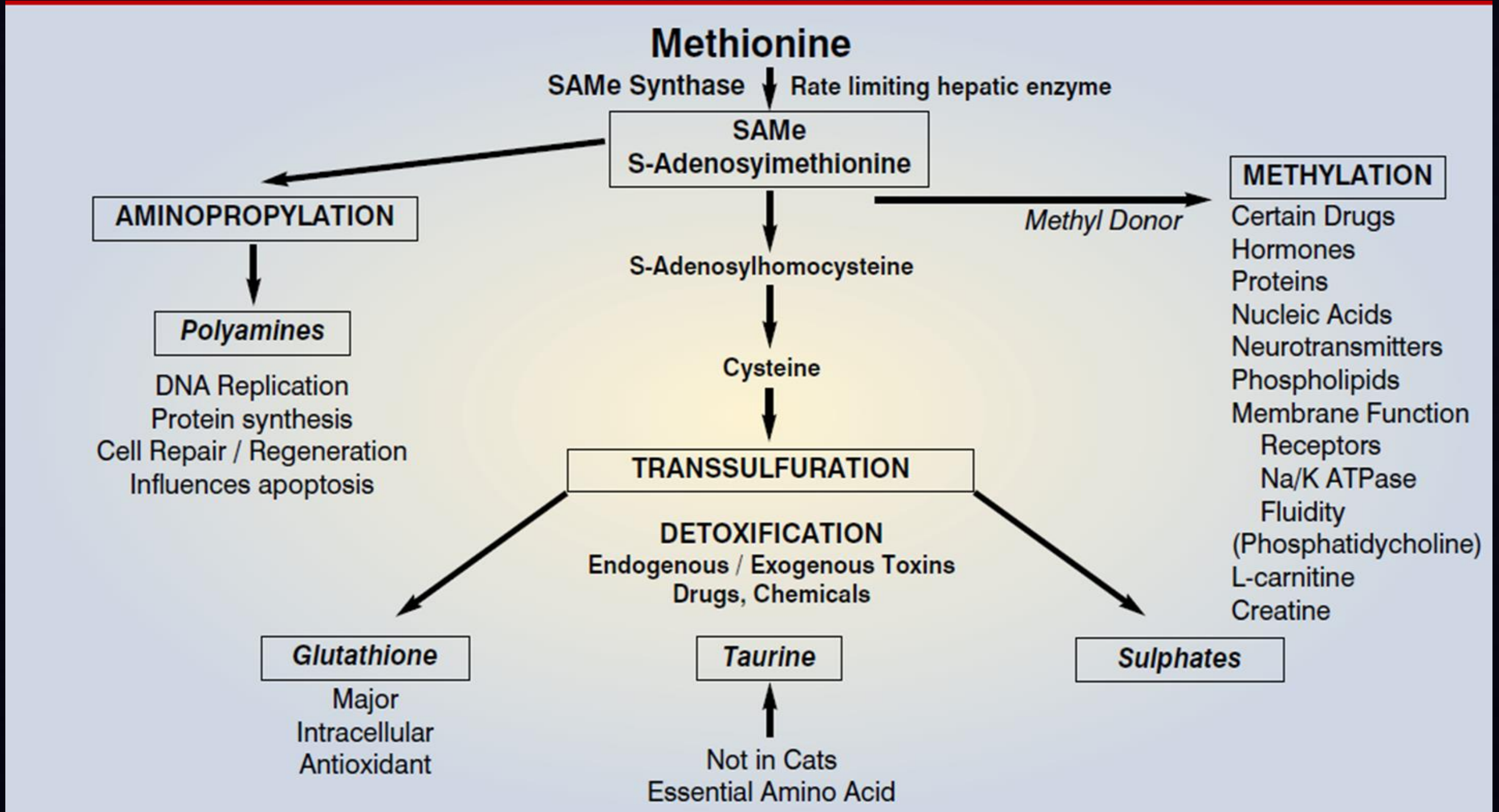
ANTIOXIDANTS

- Glutathione depletion occurs with 50% of canine hepatopathies
- Oxygen free radicals and oxidative stress
  - Initiate/perpetuate most hepatobiliary diseases
  - Can occur with free copper in liver cells
  - Mushroom toxicity (Amanita phalloides)
  - Inflammatory hepatopathy
    - Activated macrophages also produce free radicals
    - Most inflammatory disorders have oxidative damage

S-ADENOSYL-L-METHIONINE (SAME)

- Cytoprotective benefits in hepatobiliary disease
  - Increases GSH levels
  - Improves membrane fluidity and stability
  - Modifies cytokine expression
- Modulation of bile acid induced apoptosis
- SAMe is antiproliferative and pro-apoptotic in neoplastic hepatocytes
- Dose: 18-20 mg/kg orally per day
  - Empty stomach at least one hour before feeding
  - Length of treatment varies
  - Could be lifelong
- Should not be used if severe hepatic encephalopathy




Methionine
SAMe Synthase
Rate limiting hepatic enzyme
SAMe
S-Adenosyimethionine
AMINOPROPYLATION
Polyamines
DNA Replication
Protein synthesis
Cell Repair / Regeneration
Influences apoptosis
S-Adenosylhomocysteine
Cysteine
TRANSSULFURATION
Methyl Donor
METHYLATION
Certain Drugs
Hormones
Proteins
Nucleic Acids
Neurotransmitters
Phospholipids
Membrane Function
Receptors
Na/K ATPase
Fluidity
(Phosphatidycholine)
L-carnitine
Creatine
DETOXIFICATION
Endogenous / Exogenous Toxins
Drugs, Chemicals
Glutathione
Major
Intracellular
Antioxidant
Taurine
Not in Cats
Essential Amino Acid
Sulphates

MILK THISTLE (SILYBIN/SILYMARIN)

- Protective influence in liver intoxication
- Antioxidant/anti-inflammatory effect
- Inhibits liver toxin binding
- Promotes choleresis
- Increases hepatic glutathione
- Increases protein synthesis and hepatocellular regeneration
- Suppresses fibrogenesis, promotes fibrinolysis
- Iron chelator
- Dose
  - 20 to 50 mg/kg/day orally
  - 4-8 mg/kg/day if compounded with phosphatidylcholine (Marin, Denamarin)

VITAMIN E

- Membrane bound intracellular antioxidant
- Protects membrane phospholipids from oxidative damage
- Stops free-radical induced chain reactions
- Antiproliferative effects on vascular smooth muscle
- Inhibitory effect on platelet aggregation and adhesion

- Dose - 150 IU to 400 IU orally, once to twice a day
- No major side effects
  - Overdose inhibits Vit K, decreases prothrombin function
  - Unknown mechanism

URSODIOL

- Antioxidant
  - Thought to displace more toxic, hydrophobic bile acids
  - Diminishes the ‘detergent-like’ action of hydrophobic bile acids
    - Hepatocyte membrane injuries
    - Oxidative damage and induction of apoptosis
- Antifibrotic
- Choleretic and anti-inflammatory
  - Bile thinning effect
  - Aids in toxin elimination
- Can help dissolve gall stones
- Immunomodulatory effect by increasing glutathione

URSODIOL

- Indications
  - Chronic cholestatic, inflammatory liver disorders
  - Disorders complicated by “sludged” bile
  - Cholelith dissolution
- Dose - 10 - 15 mg/kg per day PO SID or divided BID
  - Should be given with food
  - Should not be given to dogs with complete extrahepatic biliary obstruction
    - Is this really true?
  - Length of treatment may vary
  - Could be lifelong
- Adverse Effects: diarrhea, constipation, vomiting

ANTIMICROBIALS

- Ideally, based on culture and sensitivity
- Indicated while awaiting culture result
- Acute hepatitis of an infectious origin
  - Amoxicillin-clavulanate 12.5 mg/kg BID
  - Enrofloxacin 5mg/kg BID
  - Metronidazole reduced dose 7.5mg/kg BID (hepatic metabolism)
- Lepto
    - Ampicillin 20–30 mg/kg q6–8h
    - Amoxicillin 20–30 mg/kg BID-TID
    - Doxycycline 5 mg/kg BID x 2 weeks
      - Hepatotoxic?

METRONIDAZOLE

- Anaerobic activity
- Immunomodulatory activity
- Dose-dependent antioxidant effect
- Synergistic with prednisone
- Adverse effects
  - Anorexia Vestibular neuro signs
    - resolve within 1 week of drug discontinuation or dose adjustment

GLUCOCORTICOIDS

- Indications
  - Immune-mediated etiology
  - In acute insult
    - Anti-fibrotic
    - Choleretic effects
- Prednisolone (oral)
  - 2-2.2 mg/kg SID initially
  - Lowest effective dose determined
  - 25% current dose reduction in 2-week intervals
- Chronic therapy
  - Prednisolone 0.5 mg/kg daily or 1 mg/kg EOD
- If ascites or edema
  - Use steroid without mineralocorticoid effect
  - Dexamethasone
  - Divide the pred dose by 7-10 for dex dose
- For adverse GI effects
  - Sucralfate 0.25-1g PO BID / TID
  - Omeperazole: 0.5 mg/kg PO SID
- If PU/PD is intolerable
  - Dexamethasone
- ↑Catabolism
  - Increase calories

STEROID DOSING

Large breed dogs

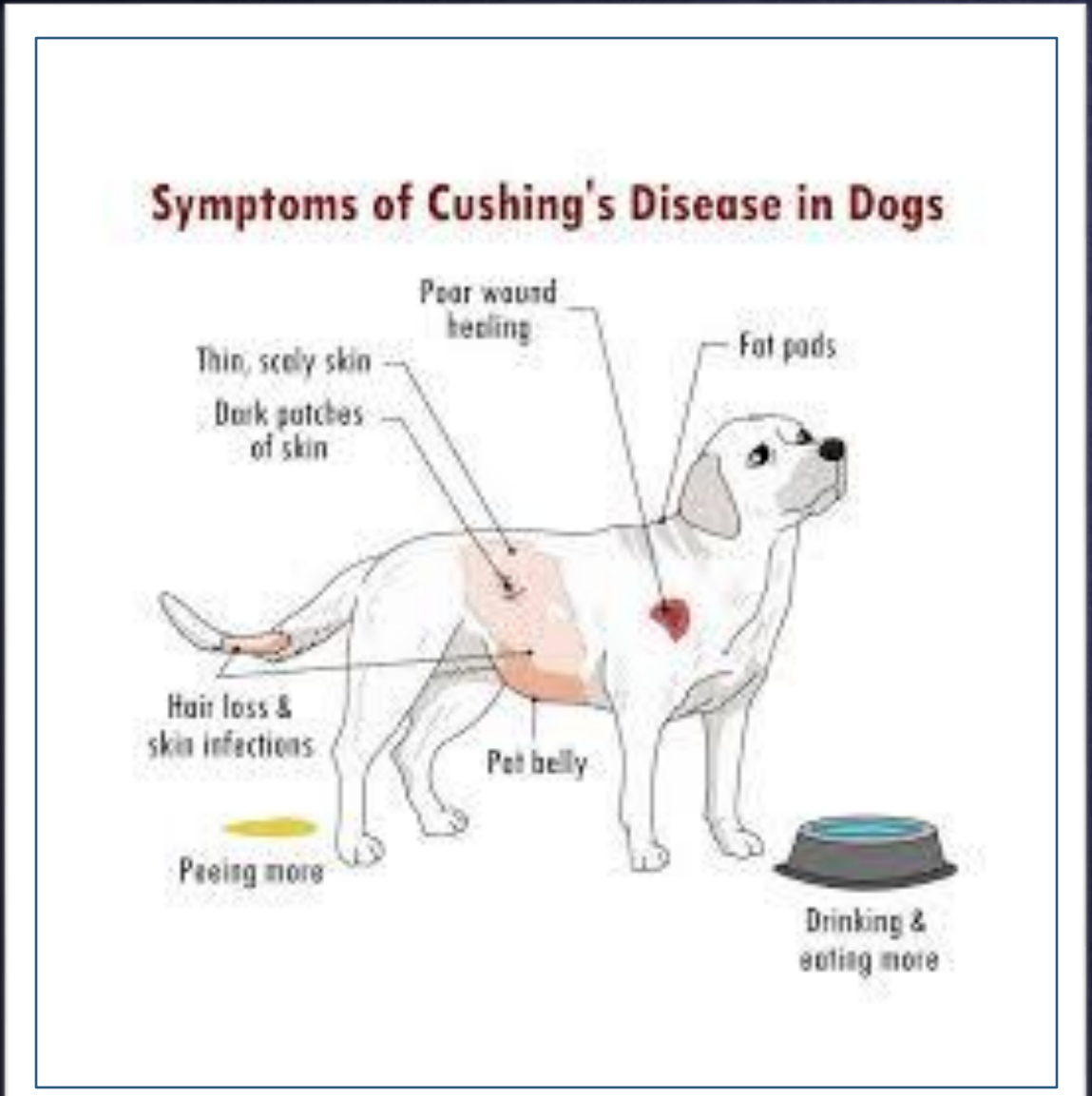
- Dogs >25 kg
- 40-50 mg/m2 PO q 24 hr
- Never exceed 40-60 mg total per day

Converting the dose from pred to dex

- Wt = 10 kg
- Divide pred dose by 7-10
- Pred dose 2 mg/kg = dex dose 0.2-0.28 mg/kg
- Pred dog 20 mg = dex dose 2-2.8 mg

BENEFICIAL EFFECTS OF STEROIDS

- Antifibrotic → ↓Collagen Synthesis
- Anti-inflammatory
  - ↓Non-specific active inflammation
  - ↓Circulating lymphocytes
  - ↓Lymphocyte replication
  - ↓Neutrophil chemotaxis
  - ↓Autoimmune injury
  - ↓Production prostaglandins
  - ↓Production leukotrienes
- Appetite Stimulant
- Promotes gluconeogenesis
- Choleretic effect
- Erythropoietic
- Mood alteration



ADVERSE EFFECTS OF STEROIDS

- Sodium & water retention
- ↑Susceptibility to infection
- ↑Catabolism, muscle wasting
- Gastroenteric ulceration
- Liver enzyme induction
- ↑ Lipolysis
- Suppressed pituitary/adrenal axis
- Polyuria, polydipsia
- Behavior change

AZATHIOPRINE

Beneficial Effects

- Faster reduction of steroid
- Lower dosages of each medication
- More effective in modifying T-lymphocyte than B-lymphocyte function

Dose

- In combo with prednisolone
- 1.0 - 2.0 mg/kg PO SID x 5-7 days, then EOD.

Adverse Effects

- Bone marrow toxicity
  - Neutropenia
  - Thrombocytopenia
- GI signs

Monitoring

- CBC and chemistry panel
  - every 2 to 3 weeks for the first 2 months
  - Then monthly thereafter

ZINC

- Antifibrotic/antioxidant effect
- Hepatoprotectant effect against toxins
- Prevents intestinal absorption of copper
- Increases intestinal and hepatic copper chelators (metallothionein)
- Maintain the urea cycle
- Zinc gluconate PO 1.5-3.0 mg/kg TID
- Zinc acetate 50-200 mg per day (> 15 kg sized dog) is given in 2 divided doses, 30-60 minutes before meals
- Goal - serum zinc concentrations 200-500 ug/dL
- Hemolysis - >1000 ug/dL

D-PENICILLAMINE

- Indication: primary or secondary excess copper accumulation
- Chelation
  - Bind hepatic copper and excrete it in bile
  - Detoxify hepatic copper via Metallothionein.
- Anti-inflammatory
- Anti-fibrotic effects
- Dose 5-14 mg/kg PO BID
- Adverse effects
  - GI side effects (vomiting and anorexia)
    - Gradual dose escalation
    - Concurrent use of anti-emetic
    - Low dose use of appetite stimulant
- Co-treatment of Zinc and penicillamine is CONTRAINDICATED.

HEPATIC DIETARY RECOMMENDATIONS

- Not all patients need a liver diet!
- Protein restriction 17-22%
  - Evidence of protein intolerance (i.e. HE)
  - Additional comorbid condition requiring restriction (i.e. PLN, renal ds.)
- Copper restriction
  - If documented copper hepatopathy on biopsy
  - Possibly for breeds known to accumulate copper?

QUESTIONS TO ASK YOURSELF…

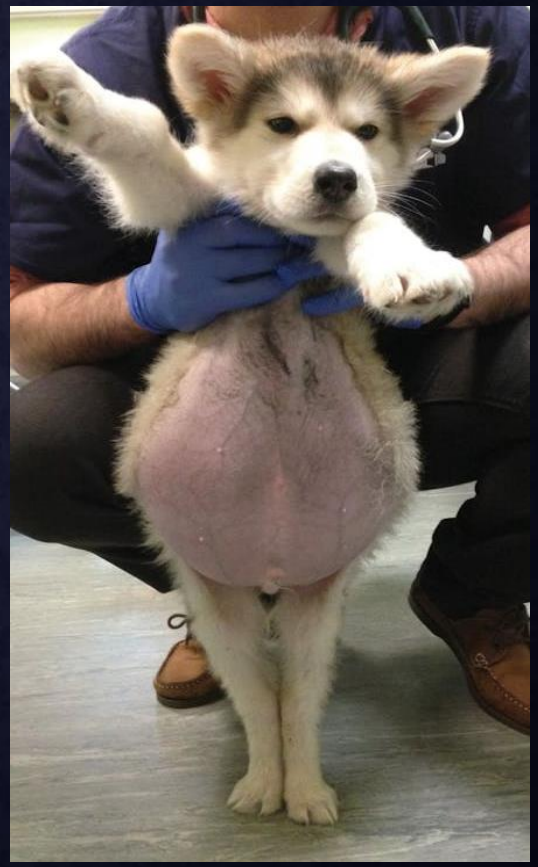
- What is the patient's age and breed?
  - Many breed associated hepatopathies
    - Labrador Retriever
    - Dalmatian
    - Doberman Pinscher
    - Terriers – Skye, Bedlington, Westie
    - Cocker Spaniel
    - Scottish Terrier
  - PSS/MVD
    - Maltese, Yorkie, Min. Schnauzer

MORE QUESTIONS TO ASK…

- What medications is the patient on?
  - Enteral
    - Ask about supplements
  - Parenteral
    - Topicals
    - Inhaled
- WHY was the bloodwork performed in the first place?
- Is the elevation repeatable?

MORE QUESTIONS TO ASK…

- Any clinical signs of liver dysfunction?
- Other biochemical changes?
  - Hepatic dysfunction on bloodwork
    - Elevated bilirubin
    - Low cholesterol, BUN, hypoalbuminemia
    - Isosthenuria
  - Pancreatic enzyme elevation
  - Anemia
- Any evidence of other systemic illness? Cushing’s disease?



“HOLLY” 8 YR FS SCOTTIE

- Presented for dental prophy
  - Normal clinically
- Initial ALKP 1650 U/L, USG 1.034
- Dental with extractions was performed
  - Post-procedural Clavamox for 10 days
- ALKP 30 days later was 930 U/L
  - Maybe she’s improving?
- ALKP 4 months later was 2130 U/L!
  - Owners now say maybe she has polydipsia now

NEXT STEPS?

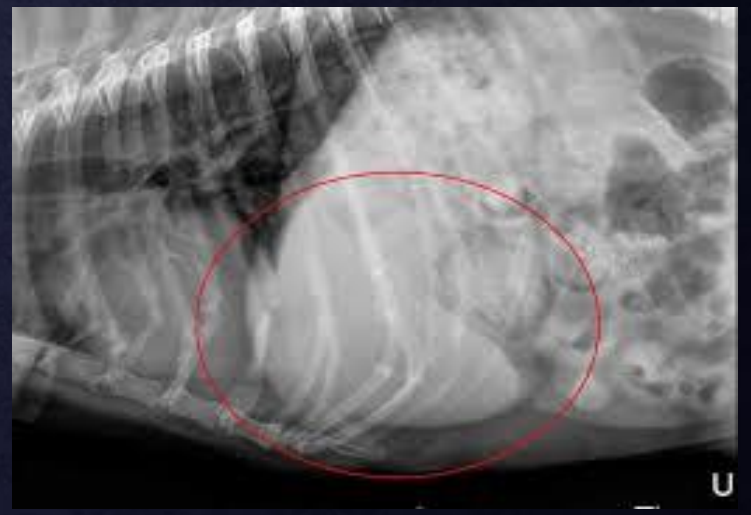
- UA
  - USG 1.024
  - No proteinuria
- Abdominal ultrasound
  - Subjective mild hepatomegaly
- Urine cortisol creatinine ratio
  - 20 (normal)
- Bile acids
  - WNL
- Thyroid panel
  - WNL

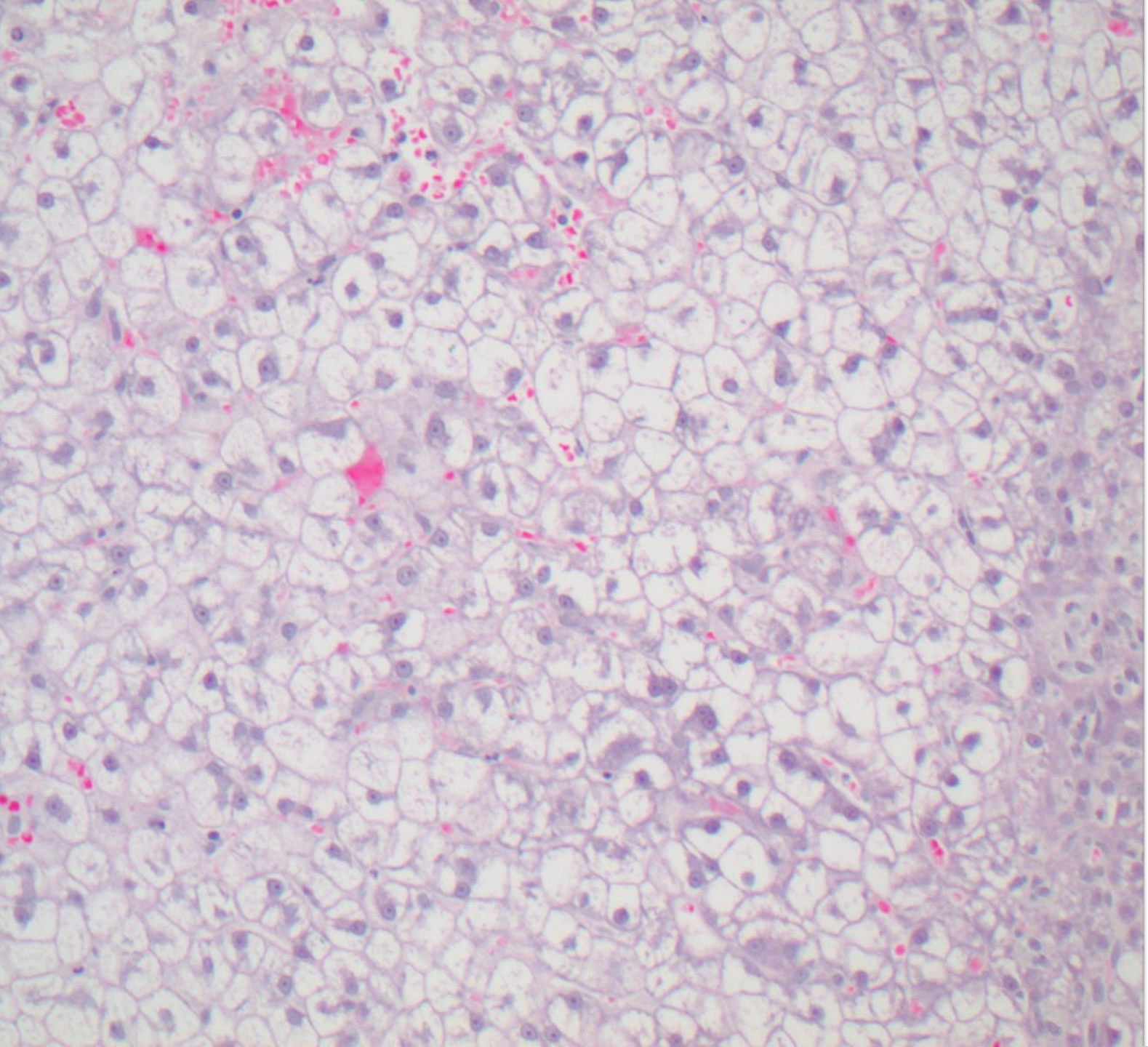
Trial therapies

- Denamarin
- Ursodiol

Recheck

- ALKP 2326 U/L





“HOLLY” 8 YR FS SCOTTIE

- Liver biopsy:
  vacuolar hepatopathy
- Liver and bile culture:
  negative
- Cooper level:
  normal

VACUOLAR HEPATOPATHY (VH)

What is it?

- Vacuoles in the cytoplasm of hepatocytes
- Air, water, fat, or glycogen

What are the clinical signs?

- None
- Only signs related to underlying cause

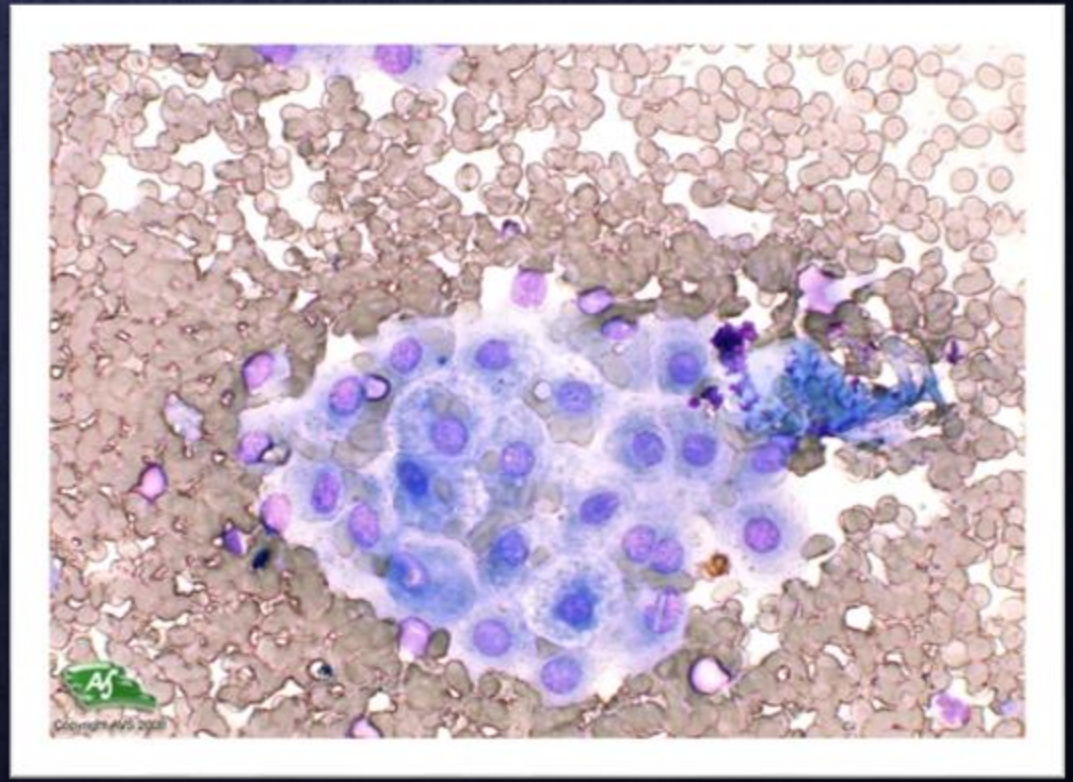
Why does it happen?

- Steroid induced
- Secondary VH
  - Endocrine disease
  - Neoplasia
  - Renal
  - Hepatitis
  - Any chronic illness/stressors
- Idiopathic

VACUOLAR HEPATOPATHY (VH)

How do you diagnose it?

- Elevated hepatobiliary enzymes
- Hepatomegaly
- Typical ultrasonographic appearance
- FNA?
- Liver biopsy

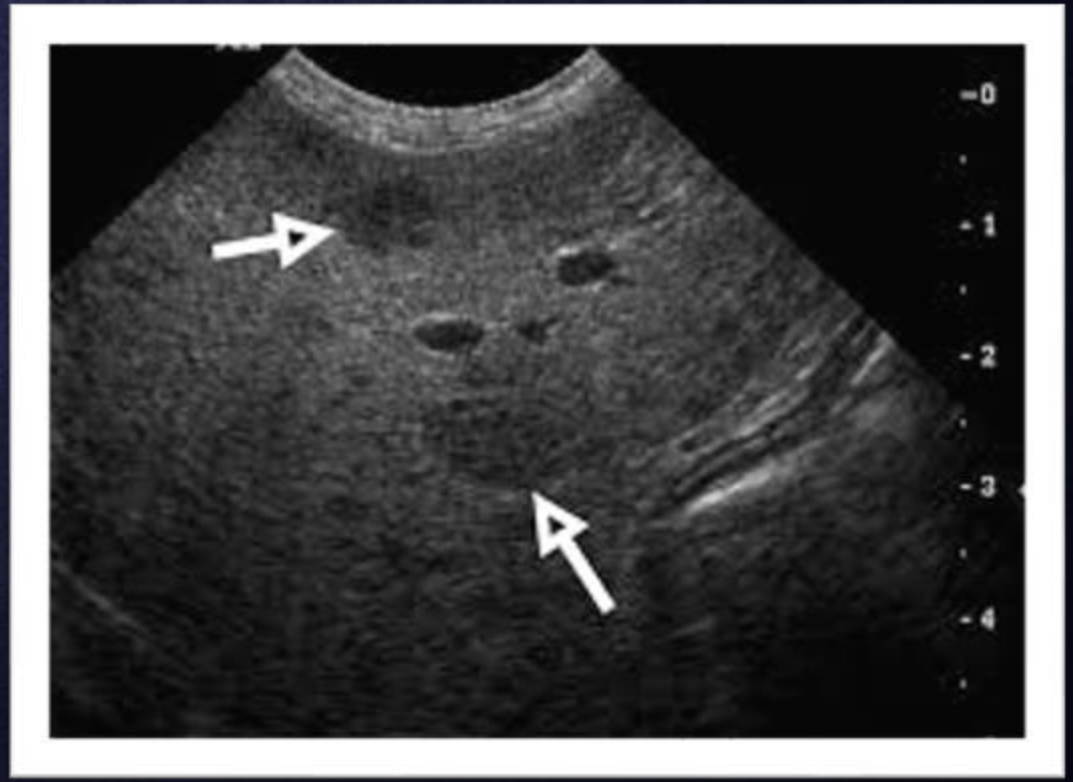


APPARENTLY HEALTHY SCOTTISH TERRIERS

- Nestor et al. 2006 JAVMA
  - Had significantly higher mean serum ALKP activity then control dogs
  - 2.4 times more likely to have a disease associated with high ALKP
- Zimmerman et al. 2010 JAVMA
  - More likely to have exaggerated adrenal panel and histological changes of VH
  - This included Scotties with AND without elevated ALKP
- Cortright et al. 2014 JAVMA
  - VH in Scotties may be linked to adrenal steroid elevation
  - Predisposition for hepatocellular carcinoma

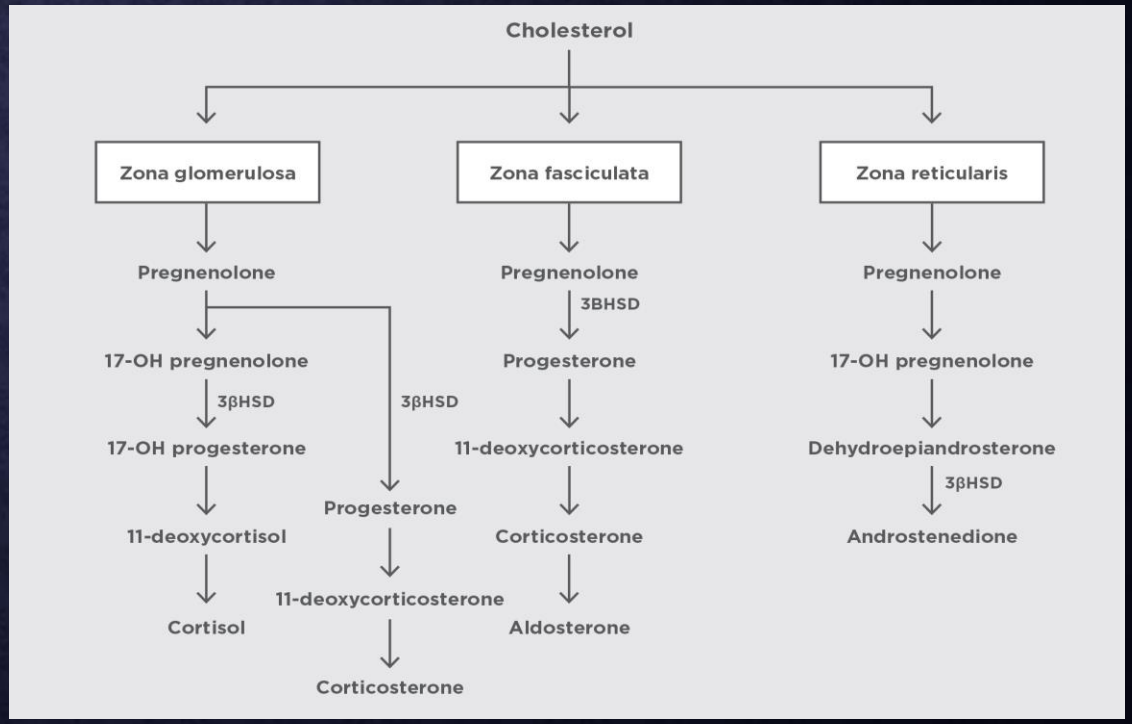
APPARENTLY HEALTHY SCOTTISH TERRIERS

- Benign diffuse vacuolar hepatopathy
- Lesion appears typical for “steroid hepatopathy”
- Clinical signs are typically absent
- Laboratory findings
  - Marked elevations of ALKP (ALP-C
  - Normal GGT, ALT, AST, and bilirubin
  - Normal serum bile acids



APPARENTLY HEALTHY SCOTTISH TERRIERS

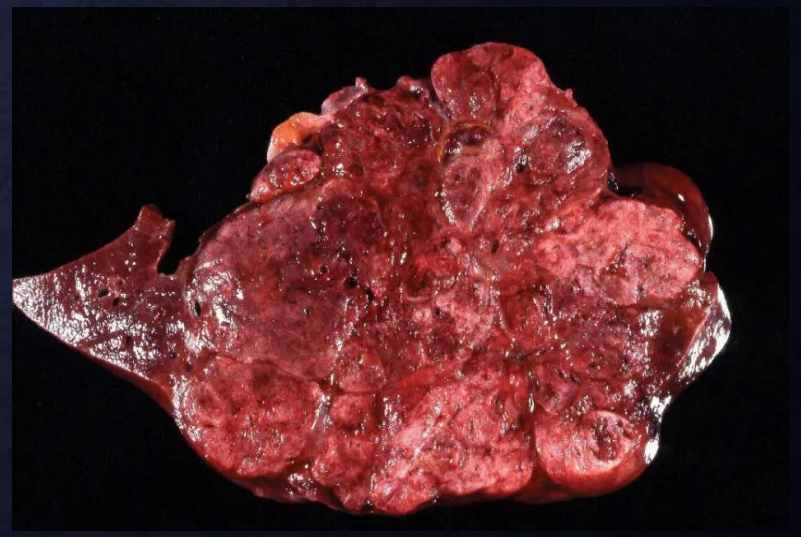
- Ultrasound
  - Adrenal glands normal in size
- Check adrenal panel at U of Tennessee
  - Most affected dogs have increases in
    - 17-hydroxyprogesterone
    - Progesterone
    - +/- other sex steroids



- These hormones could cause glycogen accumulation in the liver

APPARENTLY HEALTHY SCOTTISH TERRIERS

- Most affected dogs live out normal lives
- Hepatoprotectant therapy may help
- Treatment with Lysodren ↓ ALKP
  - Possible adrenal mechanism for the vacuolar change?
- Some dogs may become clinical for liver disease
  - Increased risk for HCC?
- Cause still unknown…



“HOLLY” 8 YR FS SCOTTIE

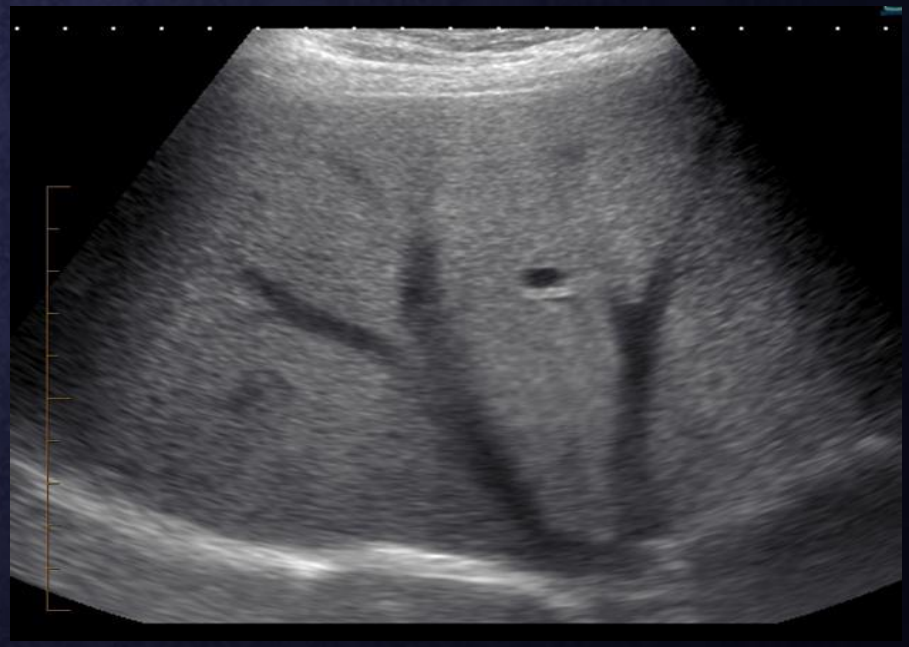
- Tennessee Adrenal panel
  - 17-hydroxyprogesterone was increased
  - Refer to trusty Tennessee Adrenal treatment worksheet
- Treatment
  - Lysodren (mitotane)
    - Conservative dose
      - 25-35 mg/kg PO, only a few days of induction
      - 25 mg/kg/week
- Recheck on treatment ALKP 367 U/L

“BRUNO” 4 YR MN DOBERMAN

- Previously dx with atopy, Valley fever (Coccidiomycosis)
  - Temaril-P, fluconazole x 4 mth
- Evidence of iatrogenic Cushing’s disease
  - 2 weeks post meds ALKP 1050 U/L
  - 1 month ~11,500 U/L (put on Denamarin)
  - 4 months ~29,000 U/L
  - 5 months ~32,000 U/L
  - Rest of bloodwork normal

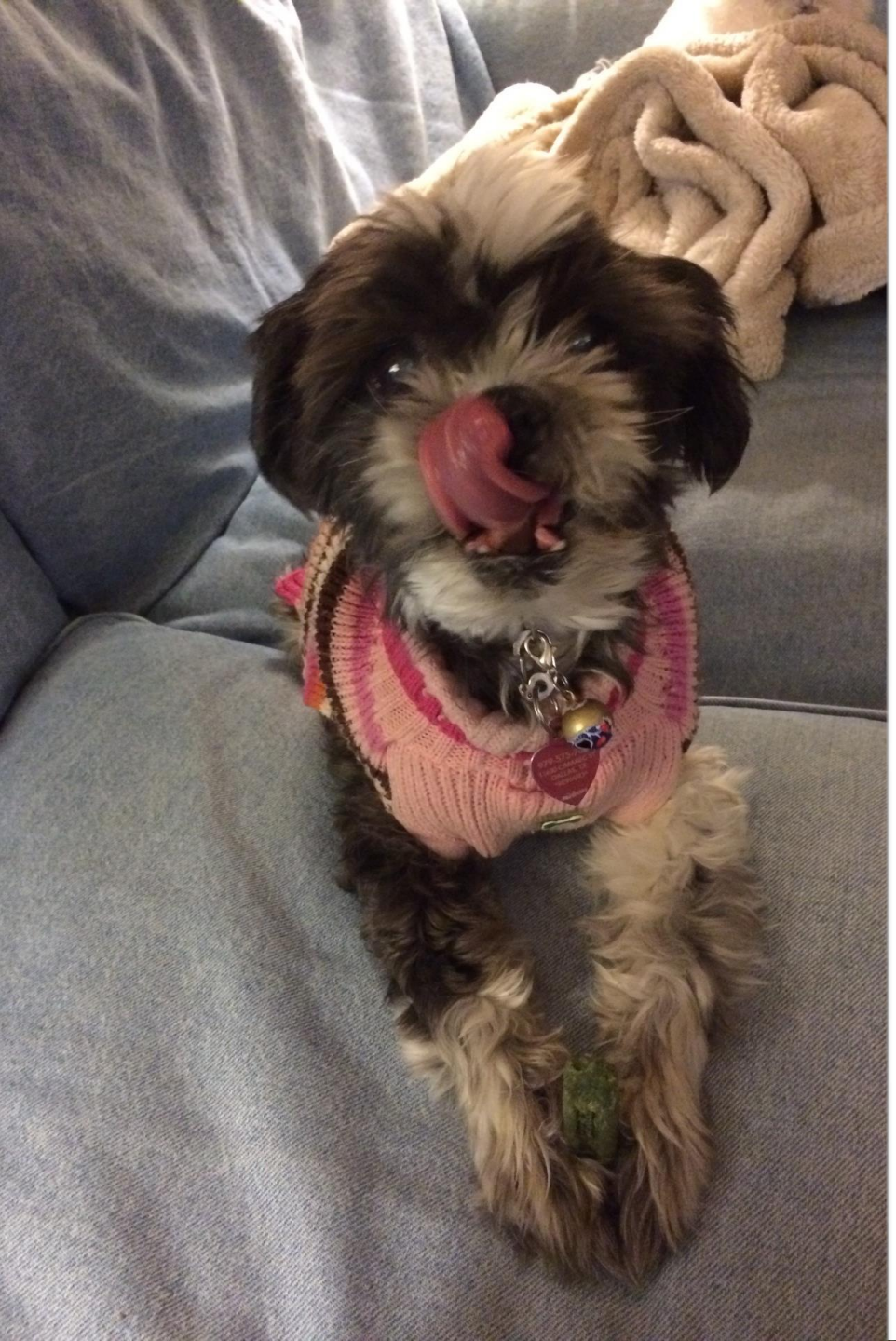
“BRUNO” 4 YR MN DOBERMAN

- Abdominal ultrasound
  - Enlarged and uniformly hyperechoic liver
  - Gallbladder WNL
- Further plan?
  - Taper off steroids!
  - Can’t stop fluconazole – Valley Fever
  - Restarted Denamarin, advised life-long use



“BRUNO” 4 YR MN DOBERMAN

- 1 month of no steroids
  - 1,335 U/L
- Owner gave 2-3 doses of Temaril-P
  - ALP 2,200 U/L
- Currently only on Fluconazole
  - ALP 750 U/L

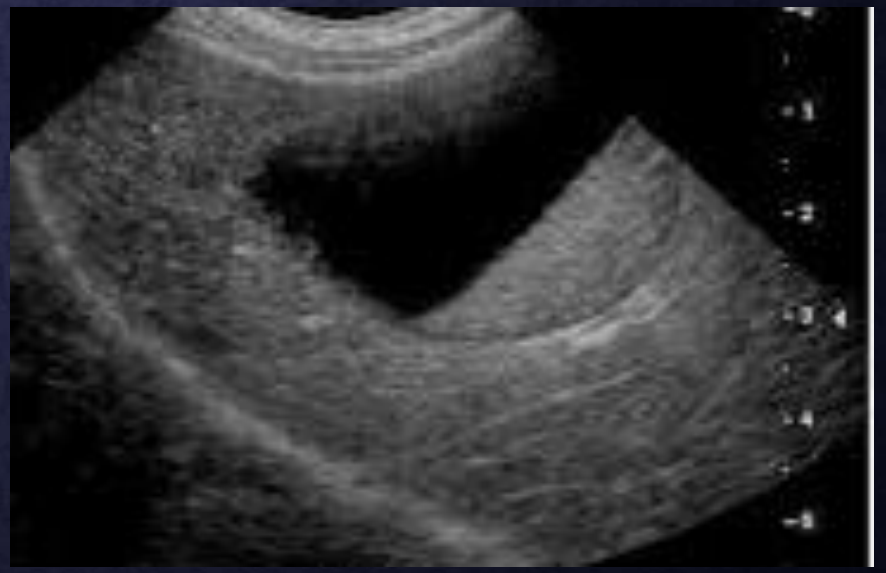


“CHARLOTTE” 9 YR FS SHIH TZU

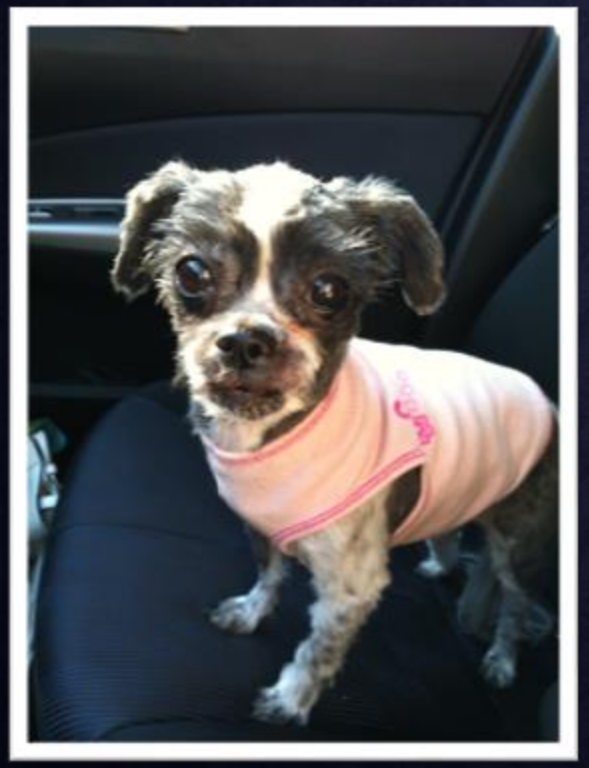
- History of IMHA
  - ALKP 190 U/L – Prior to treatment
  - Abdominal U/S – WNL
  - ALKP 540 U/L – During therapy (pred 2 mg/kg/day)
  - In remission and off of therapy for 6 mths
- Presented for recheck
  - Clinically normal
  - ALKP 840 U/L
  - Rest of CBC/Chem/UA WNL

“CHARLOTTE” 9 YR FS SHIH TZU

- UCC - WNL
- Abdominal U/S
  - “Sludge” in the gallbladder
- Therapy
  - Denamarin
  - Ursodiol



“CHARLOTTE” 9 YR FS SHIH TZU



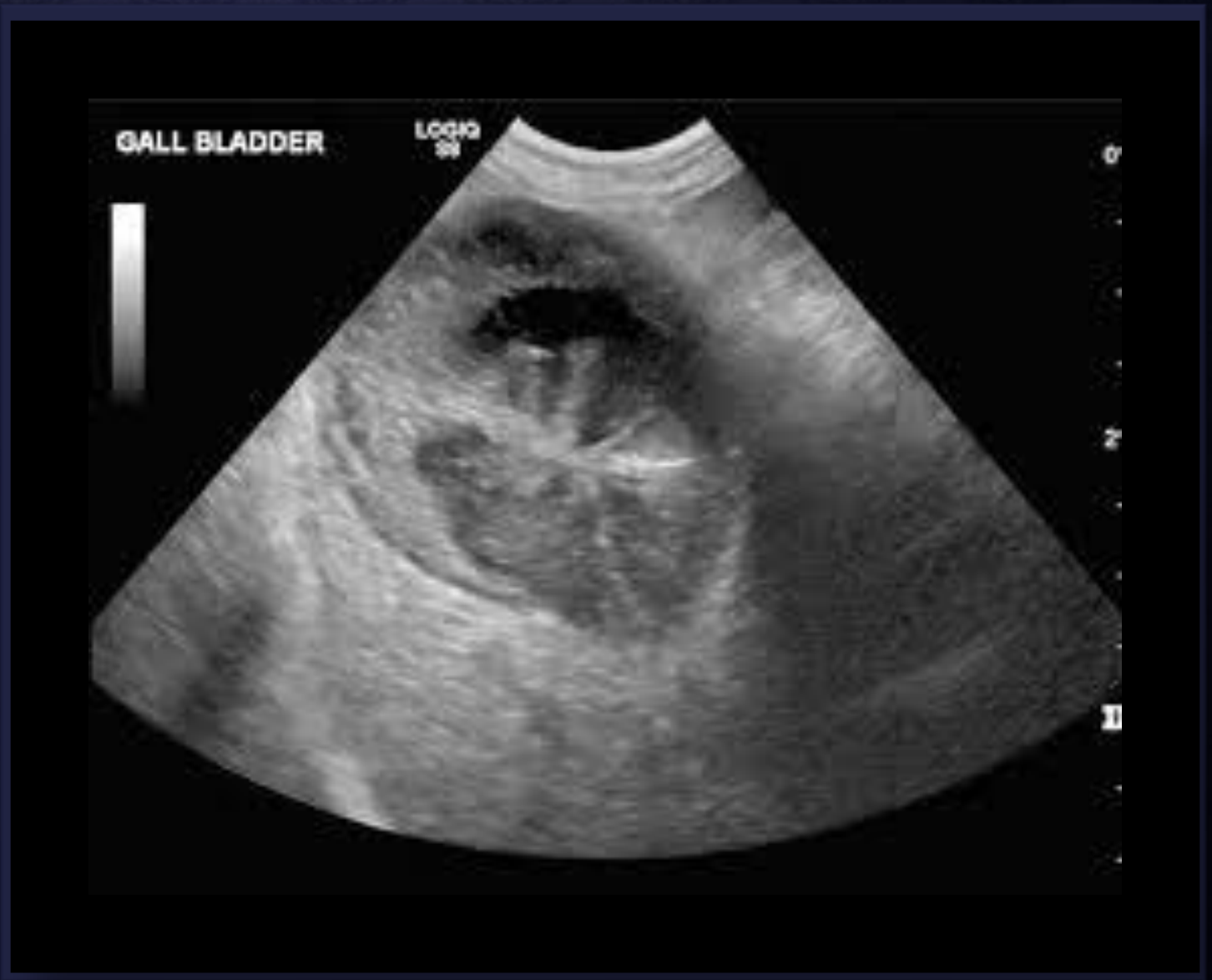
- 2 months later…
  - ALKP 1459 U/L
  - Started Clavamox and enrofloxacin
  - Continued Denamarin and ursodiol
- 3 months later…
  - ALKP 2780 U/L
  - Chol 420 mg/dL (fasted)
  - Tbil 0.8 mg/dL
  - Mild non-regenerative anemia (HCT 35%)
  - Mom says she sometimes has a picky appetite

PLAN???

- Repeat UCC ratio?
- LDDS test?
- Bile acids?
- Thyroid panel?
- PLI testing
- Recheck AUS
- Liver biopsy?

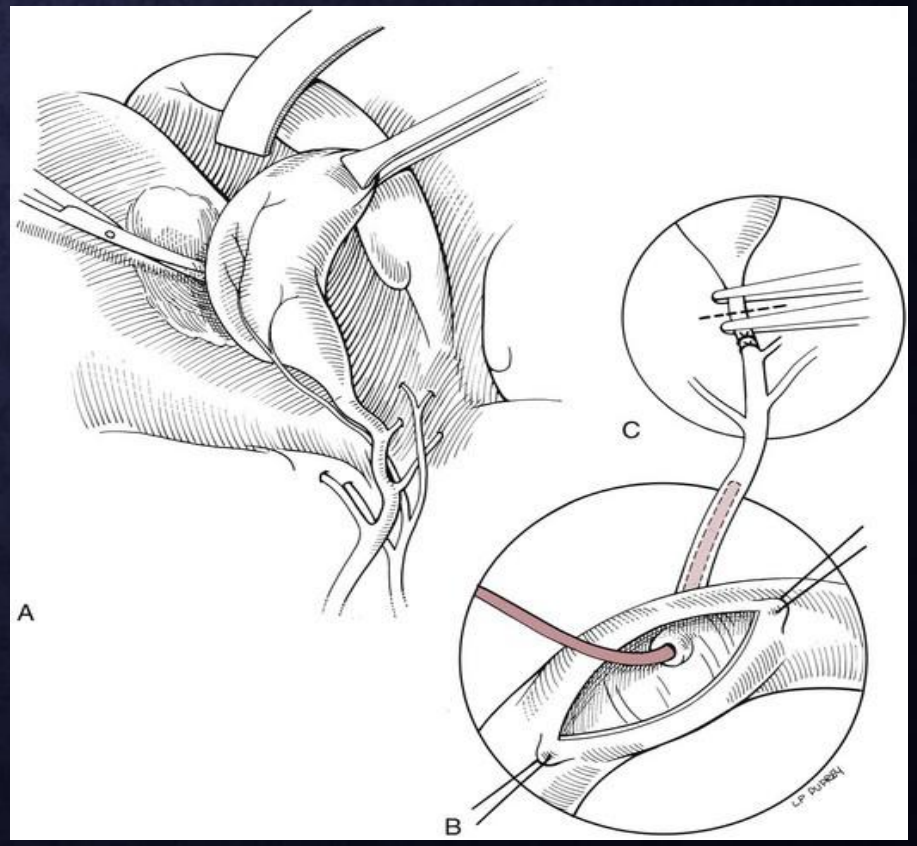
WHAT WE DID…

- Thyroid panel – normal
- Serum bile acids – normal
- Repeat abdominal ultrasound



SURGERY

- Cholecystectomy with culture of bile and liver
- Bile and liver culture
  - Negative
- GB histopathology
  - Biliary mucocele
- Liver histopathology
  - Moderate vacuolar hepatopathy



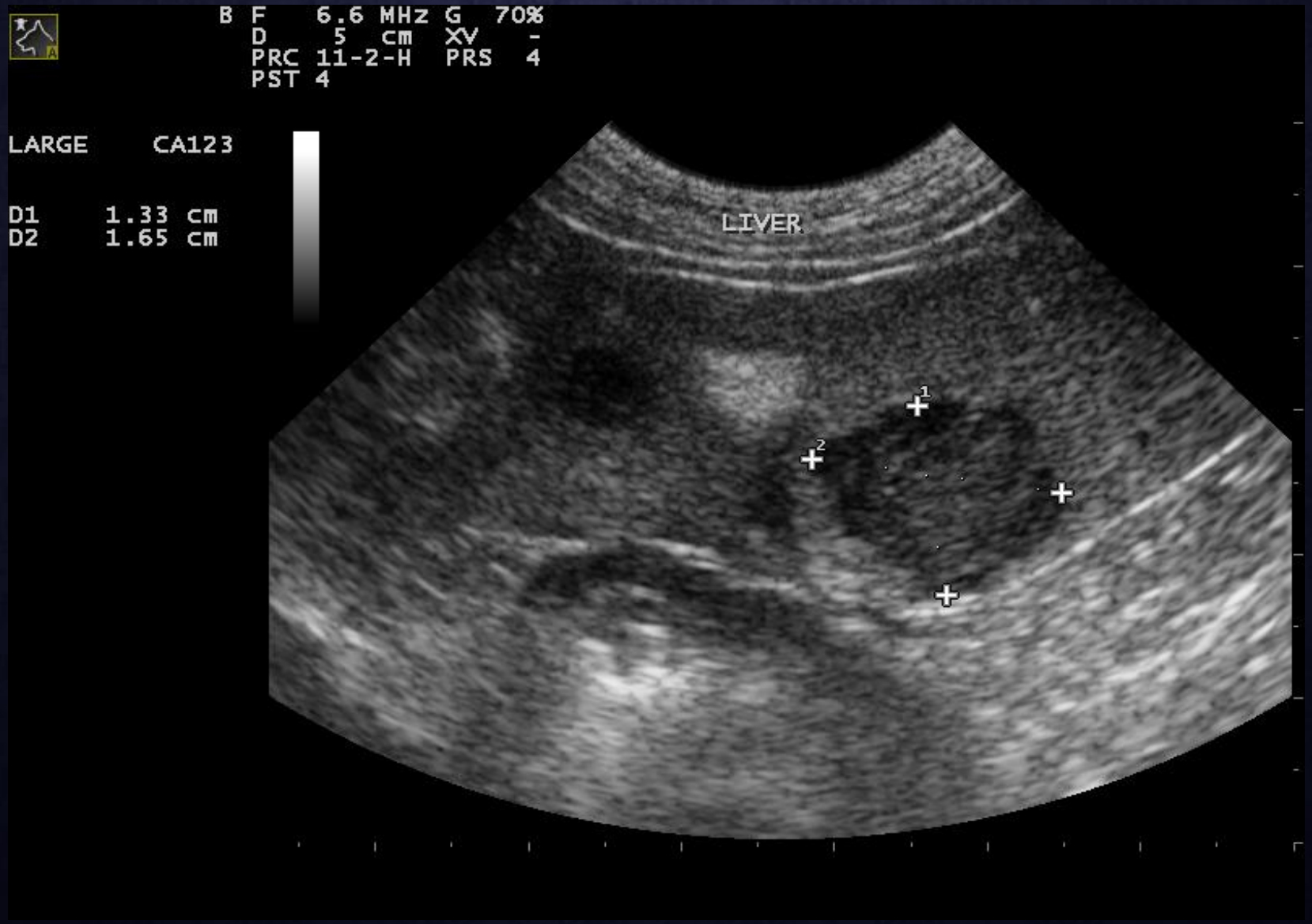
“CHARLOTTE” 9YR FS SHIH TZU

- Continued Denamarin and ursodiol
- ALKP 2 months post-op
  - 345 U/L

“PRINCESS” 10 YR FS ROTT X

- Senior wellness/vaccines
- Mild hyporexia for 2-3 months
- Eating ~ 90% of normal
- Physical exam: very tense abdomen, unable to palpate
- ALKP is 278 U/L
  - Rest of CBC/Chem/UA is normal
- Drug history
  - Prednisone – for atopy, dose 0.5 mg/kg q 24-48 hr
  - Last dose was 2 weeks ago
  - Random administration

“PRINCESS” 10 YR FS ROTT X



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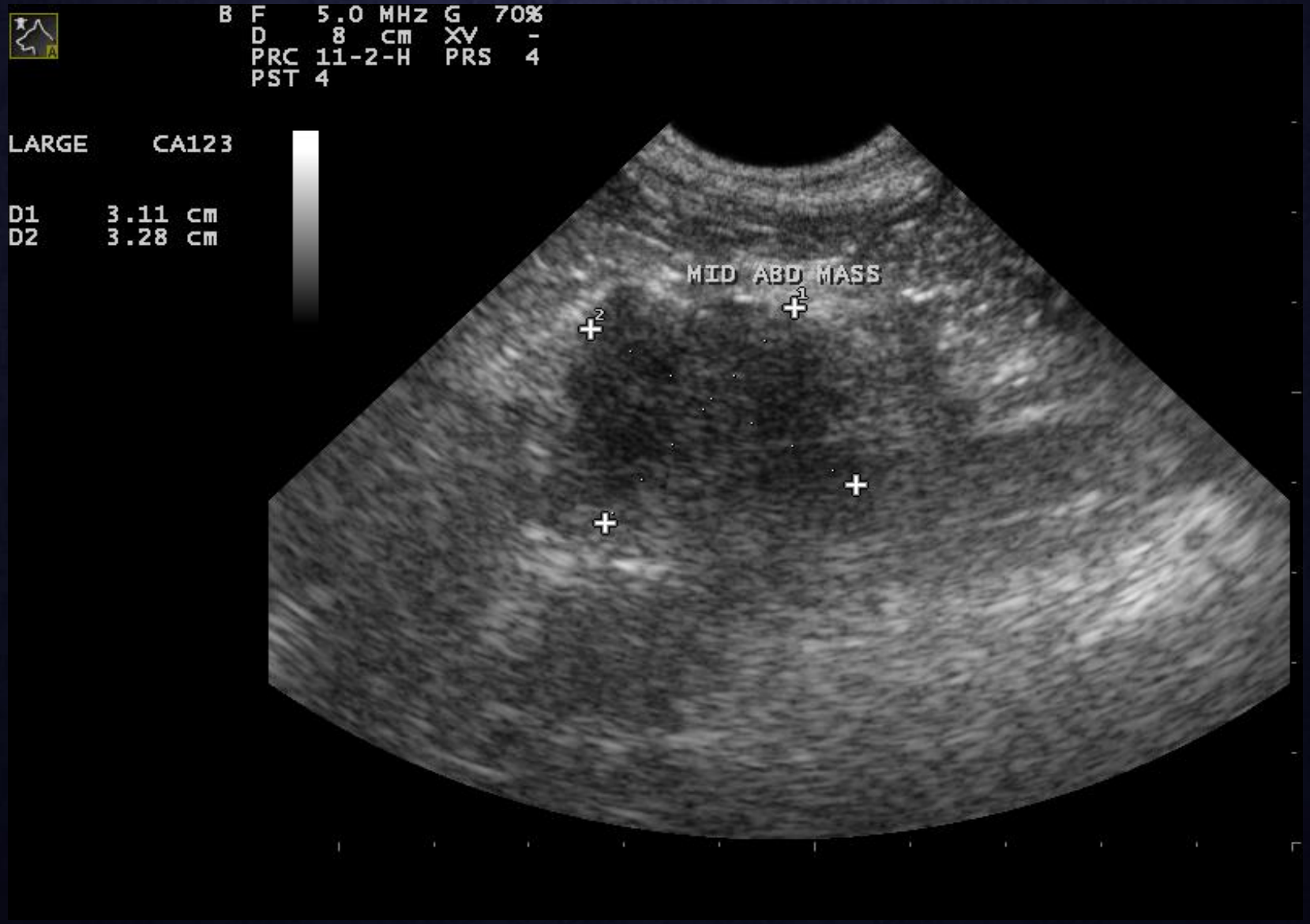

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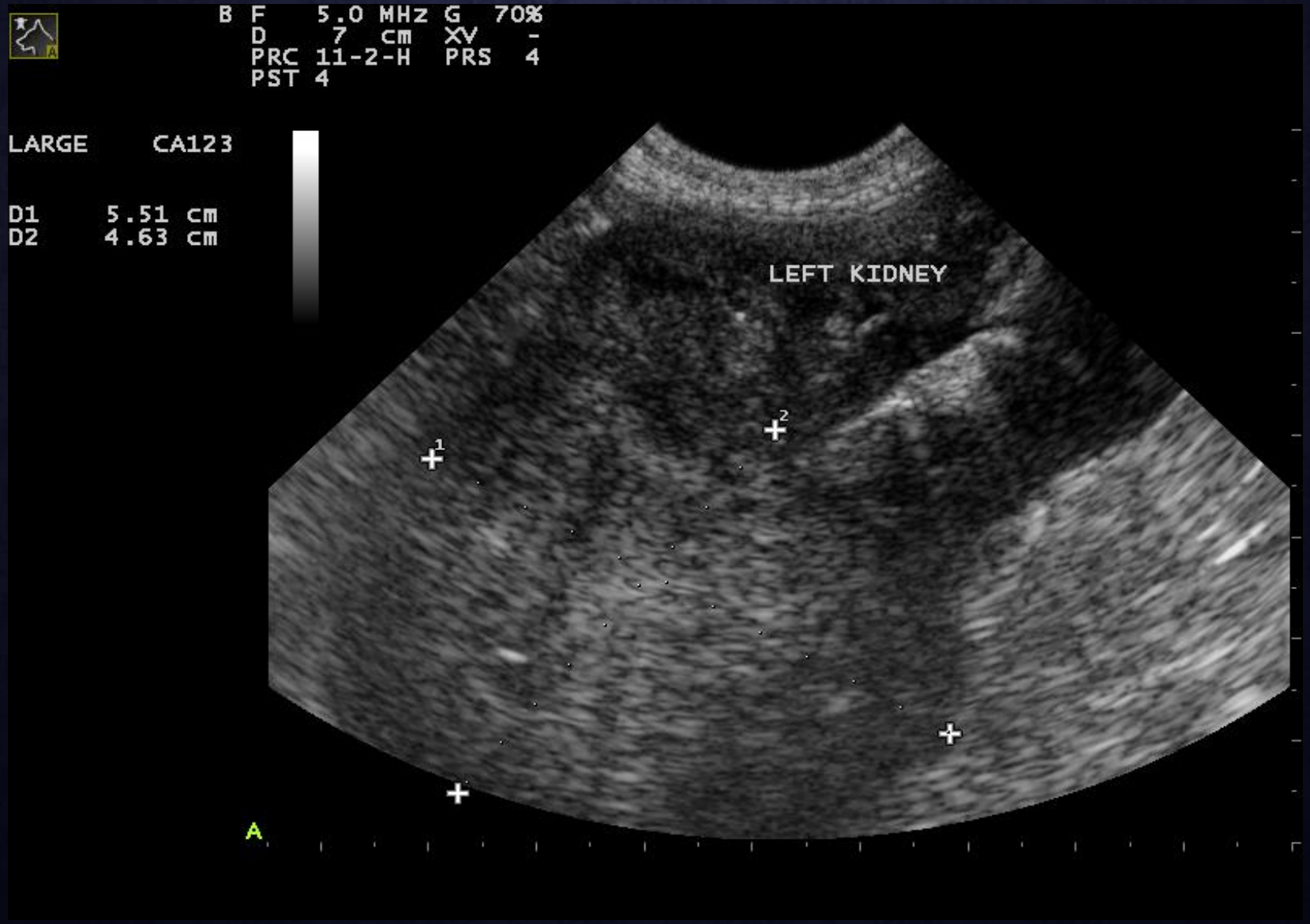

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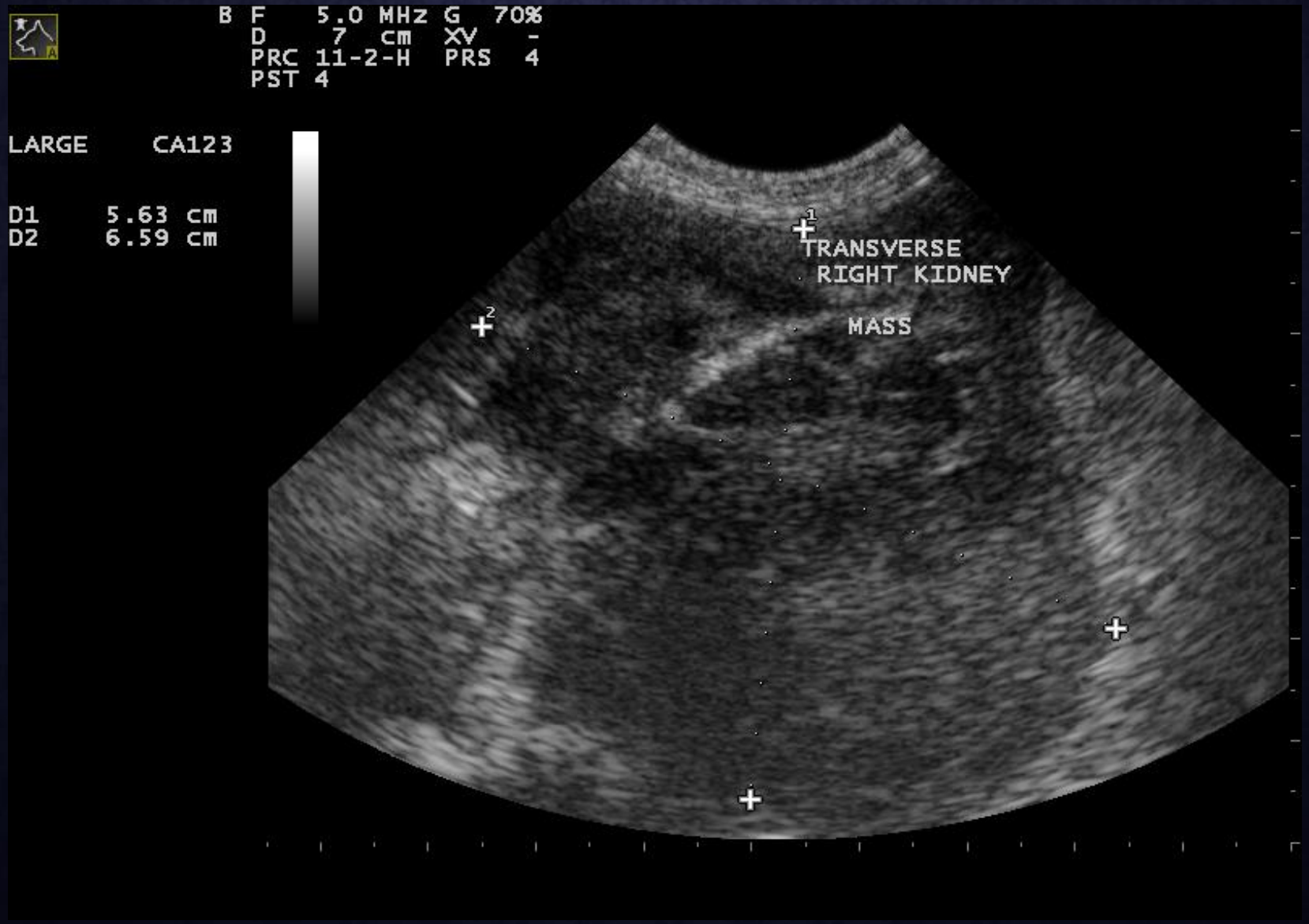
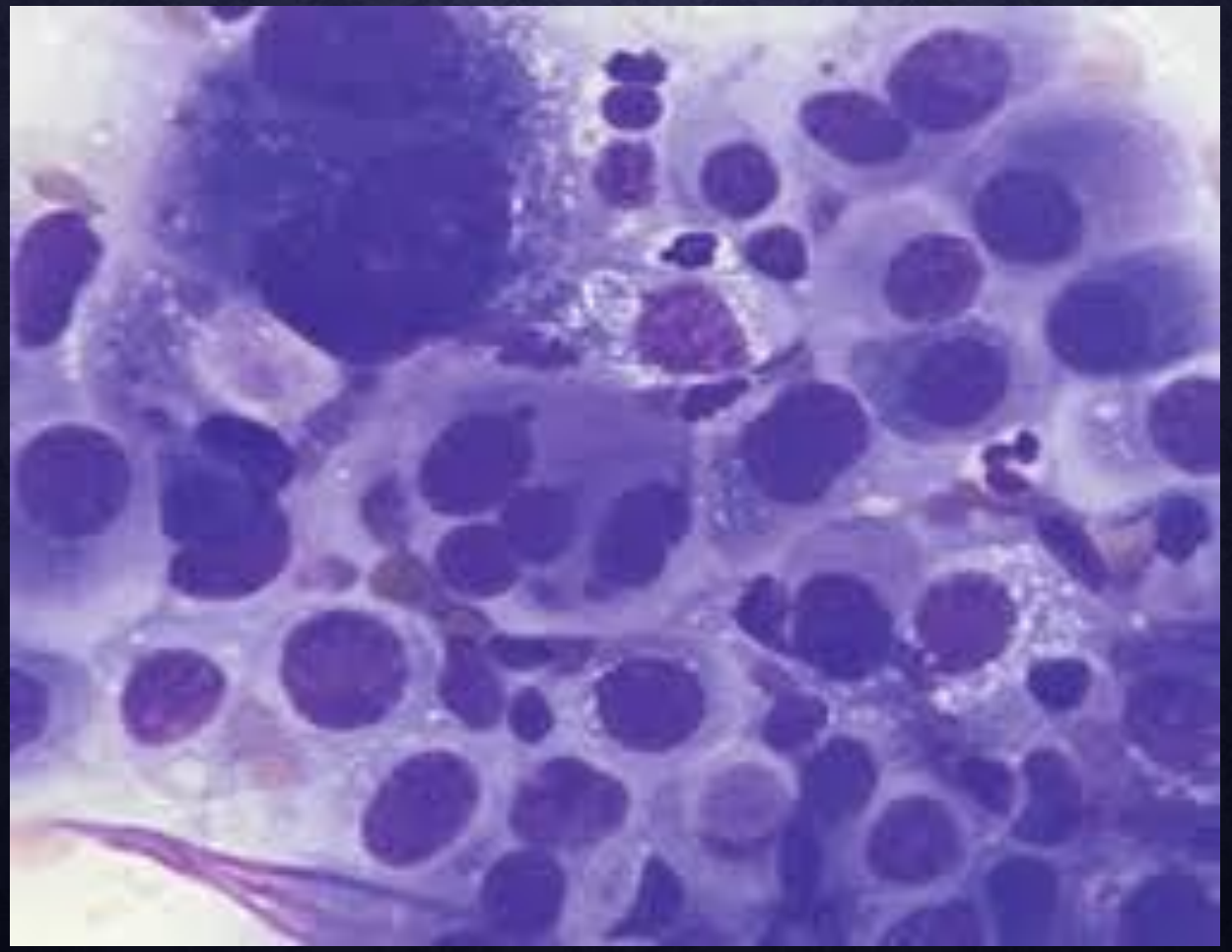


“PRINCESS” 10 YR FS ROTT X

- FNA/cytology of renal mass



“MISO” 4 YR FS BOSTON TERRIER

- Presented for minor laceration repair carpus
  - Owner unsure when it happened
  - Has been applying Neosporin to the injury
  - Looks old, severe erythema, pus, odor
- ALT 230 U/L, neutrophilia
- Rest of chemistry, CBC, UA normal

“MISO” 4 YR FS BOSTON TERRIER

- Repaired laceration
- Antibiotics
  - IV cefazolin perioperatively
  - Oral Clavamox
- Pain medication
  - Hydro injection
  - Oral tramadol

“MISO” 4 YR FS BOSTON TERRIER

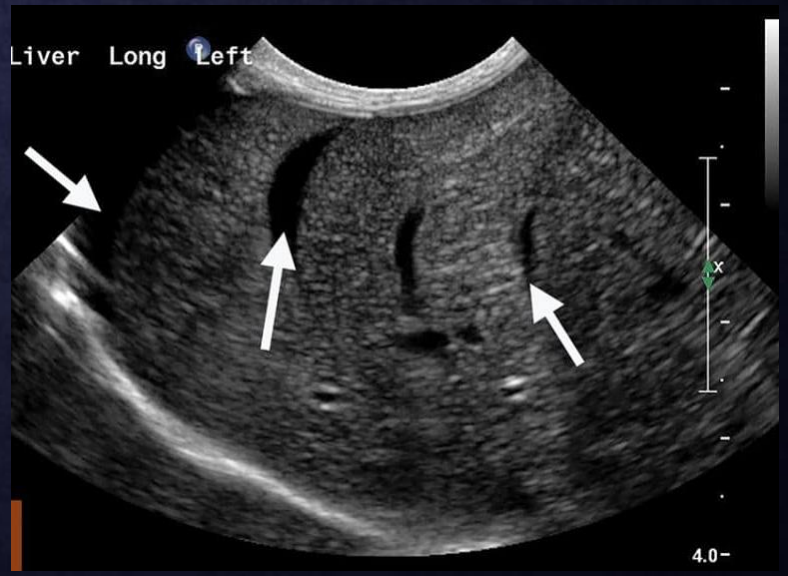
- Recheck in 2 weeks
  - Suture removal
  - Laceration completely healed
  - ALT 145 U/L
- Recheck in 1 month
  - ALT 76 U/L

“TANK” 2 YR MN MALTESE TERRIER

- Presented for annual vaccines
  - Owner reports patient is normal
  - PE: BCS 3/9, questionably “bloated” abdomen
  - Owner okayed bloodwork
  - Administered vaccines
- Bloodwork
  - ALT 331 U/L, BUN 4 mg/dL, globulin 2.2 g/dL, USG 1.011, no protein

“TANK” 2 YR MN MALTESE TERRIER

- Abdominal radiographs: microhepatia, decreased serosal detail
- AUS: scant peritoneal effusion
- Bile acids (umol/L, normal pre <15, post <30)
  - Pre – 15
  - Post – 52
- UPC ratio 0.3



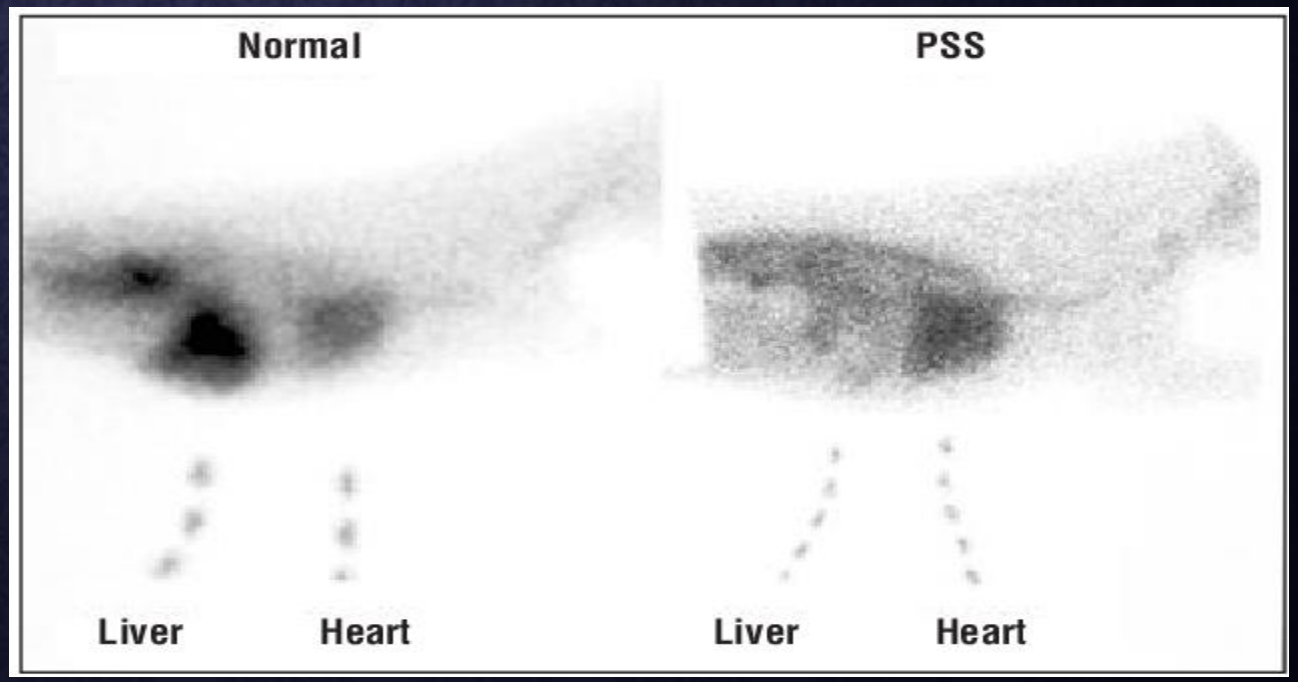
“TANK” 2 YR MN MALTESE TERRIER

- Fluid analysis: pure transudate, no etiologic agents, no neoplastic cells seen
  - congestive heart failure (venous stasis)
  - liver dysfunction/failure (hypoalbuminemia, venous stasis, and lymphatic obstruction
  - nephrotic syndrome/PLN (hypoalbuminemia)
  - PLE (hypoalbuminemia)
  - neoplasia (venous stasis and lymphatic obstruction)

“TANK” 2 YR MN MALTESE TERRIER

- Portal scintigraphy: no shunt
- Owner declined liver biopsy
- Therapeutic trial
  - Amoxicillin
  - Enrofloxacin
  - Metronidazole
  - Denamarin
  - Ursodiol

Scintigraphy



“TANK” 2 YR MN MALTESE TERRIER

- Recheck 1 month
  - Albumin 2.1 g/dL!
  - No effusion
  - BUN, cholesterol, ALT, globulin
    - All normal
  - Continued therapy another month
- Recheck 2 month
  - Albumin 1.5 g/dL, ALT 147 U/L
  - Palpable fluid wave
  - UPC ratio normal

TIME TO RETHINK?

Differentials for hypoalbuminemia

- Liver
  - liver enzymes normal, small liver, abnormal bile acids
- PLN
  - No proteinuria, cross it off the list
- PLE
  - No clinical signs of GI disease per owner

I NEED FURTHER DIAGNOSTICS?

- Repeat bile acids
  - pre 1, post 20 umol/L
- Liver biopsy? declined
- Cortisol level – normal
- GI panel – decreased folate
- Consistent with upper or diffuse SI disease
- GI biopsies? declined

- Supplemented folate
- Diet trials:
  - Hydrolyzed (2 wks, no improvement)
  - Low Fat (abdominal fluid resolved)

“TANK” 2 YR MN MALTESE TERRIER

- Recheck 2 months
  - Albumin 1.5 g/dL, rest all normal
  - Weight loss, muscle wasting
  - No fluid wave
- Owner opted to pursue endoscopy with biopsies – FINALLY!
  - Stomach – mild LP gastritis
  - Small intestine – mod LP enteritis, mod lymphangiectasia
  - Colon – mod LP colitis
- Treatment: budesonide, low fat homecooked fish/potato diet

“COPPER” 1 YR MN CORGI

- Presented for chronically mildly elevated ALT
  - First noted on pre-op screen before neuter
    - No complications with anesthesia
    - Rest of chemistry and CBC normal
- ALT currently 235 U/L
- Denamarin for 3 months
- Past history
  - Collapse while walking last summer

  Chronic intermittent vomiting every 2 weeks

  Sometimes has urinary accidents

“COPPER” 1 YR MN CORGI

- UA – USG 1.020, culture negative
- Bile acids – pre 1, post 18 umol/L
- GI panel: all normal
- AUS – normal abdomen
- Portal scintigraphy – no shunt

- Trial therapies
  - Denamarin
  - Amoxicillin
  - Metronidazole
  - Enrofloxacin

“COPPER” 1 YR MN CORGI

- Liver biopsy: minimal multifocal hepatic cellular necrosis
- Liver and bile culture: negative
- Recheck bloodwork pre-op:
  - ALT 277 U/L
  - Mild lymphocytosis 5.23 K/uL

WHAT DOES THIS MEAN?!?

NOW WHAT?

Called TAMU for consult

- Thorough owner questioning regarding toxin exposure
- Flow cytometry of peripheral blood: polyclonal, non-neoplastic, likely reactive
- Infectious disease testing
  - All fungal – negative
  - Tick panel – negative
  - Lepto titers – positive at a level consistent with vaccination, patient was vaccinated
  - Lepto PCR – negative in blood and urine

What did I miss?

ATYPICAL HYPOADRENOCORTICISM!!

- Cortisol: <0.2 ug/dL
- ACTH stimulation test
  - pre <0.2 ug/dL
  - post <0.2 ug/dL
- Treatment
  - Prednisolone 0.2 mg/kg/day
- Recheck ALT 1 month later - 55 U/L

LESSONS I'VE LEARNED

Nodules in the liver are usually not cancer.

Liver disease is often asymptomatic until the end.

Portosystemic shunting is not only a young dog disease.

Liver biopsy in end stage disease can cause patient decompensation.

Portal hypertension can cause splenomegaly.

Even cholecystocentesis done well can result in a surgical complication.

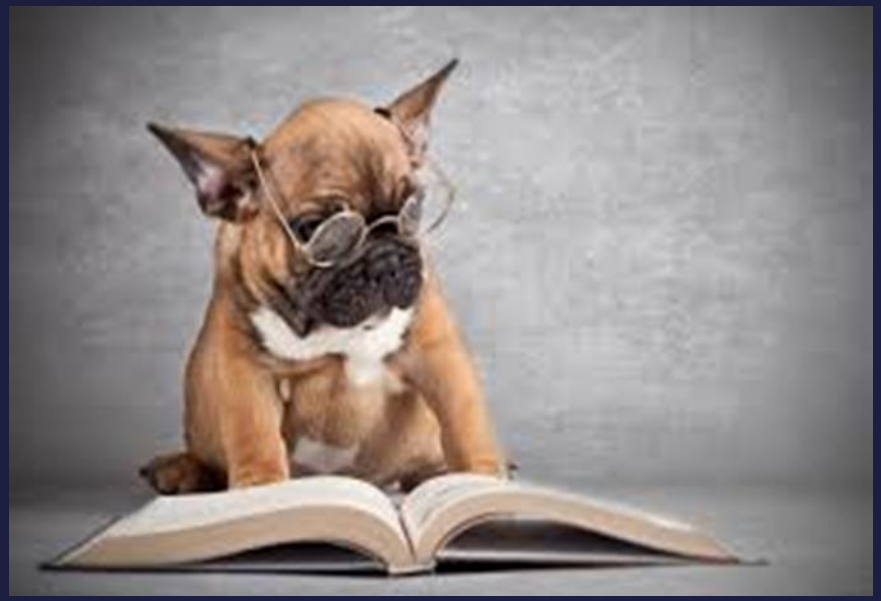
Never forget Addison's disease.

I don't really like the liver all that much.

IN CONCLUSION…

- Focus on the patients' clinical signs more than the degree of enzyme increase
- Finding a cause requires a systematic approach
- Remember your pathophysiology
- Thoroughly review the record
- Ask yourself all the questions
- Do the testing
- Develop a tailored patient plan

QUESTIONS?



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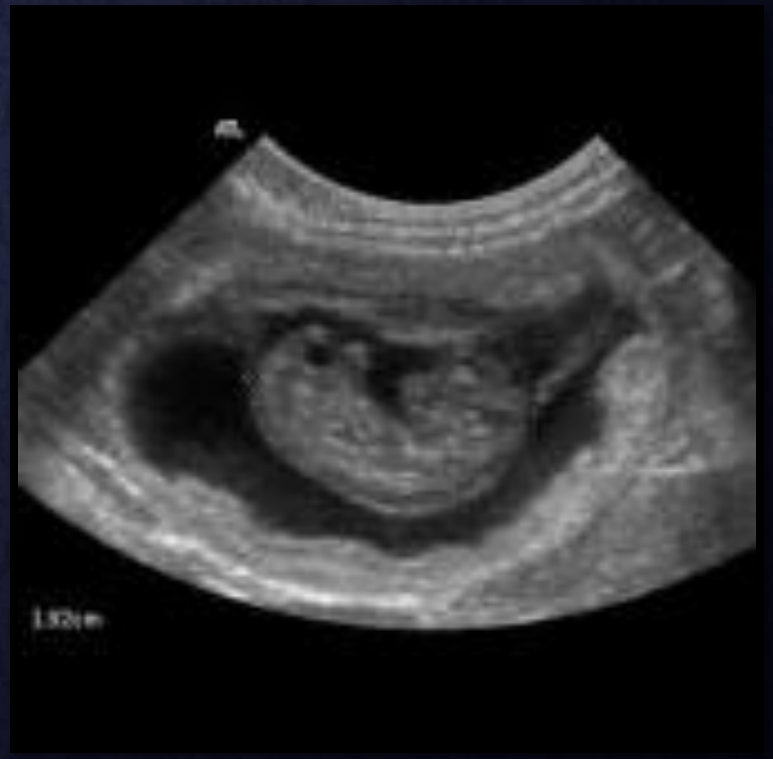
STABLE PATIENT ULTRASOUND REFERRAL PROGRAM

- Directly refer your stable patients to Diagnostic Imaging
- Ultrasound by appointment
- Once your referral request received, we reach out to you within 48 hrs
- Client to schedule an appointment via an online form
- Complete ultrasound report written by the specialist sent within 24hrs

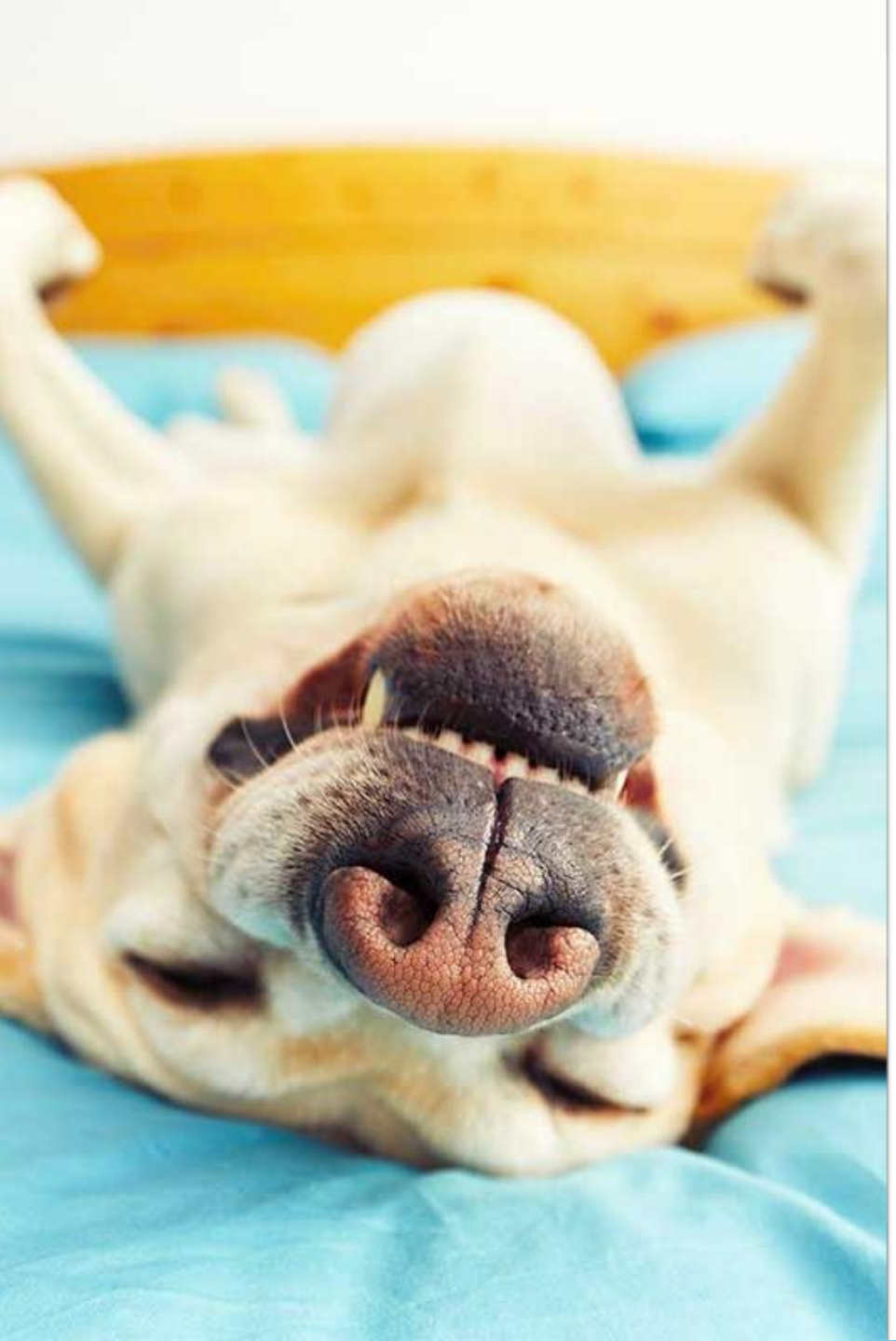


STABLE PATIENT CRITERIA

It’s important that your referred patients are in stable condition, not urgent/emergent.
Patients experiencing the following symptoms are not suitable candidates for a stable patient ultrasound referral:

- Unable to urinate
- Not eating or drinking
- Vomiting more than once in a single day
- Bleeding internally/externally (ie: low PCV, hematochezia/hematemesis)
- Lethargy
- Respiratory distress
- Unable to stand and walk

If your patient is experiencing any of the above symptoms and/or you have concerns about the urgency of imaging, we recommend that your patient be evaluated through our emergency/critical care department.

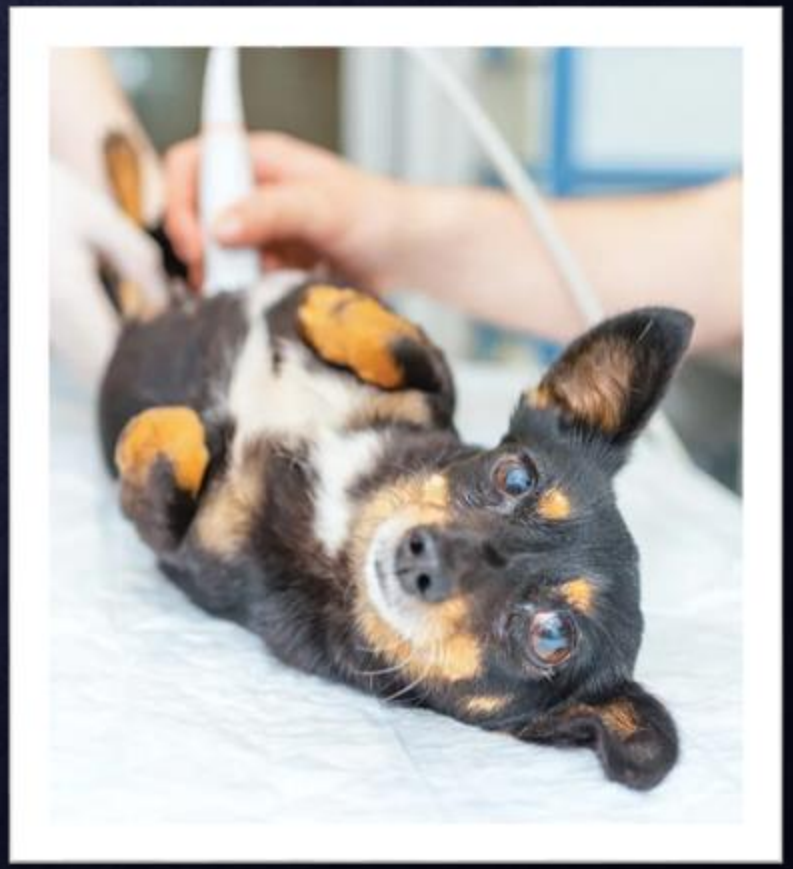


RECOMMENDED SEDATION

- We recommend some form of “chill protocol” prior to the visit.
- Ideally, patients would receive an oral sedative (with your guidance) the night before and the morning of the anticipated procedure.
- We typically recommend gabapentin and/or trazodone PO.
- Patients that are uncomfortable, extremely anxious, or uncooperative for their ultrasound may require additional injectable sedation for the ultrasound to be completed.

INFORMATION FOR YOUR CLIENTS

- We are currently able to schedule appointments the same week as the referral.
- An estimate for the cost of ultrasound will be included when we reach out for scheduling.
- Appointments generally take less than an hour.
- Patients will need to fast for 12 hr prior to the appointment unless contraindicated.
- Patients' hair will be shaved in order to perform the ultrasound.
- A detailed report will be written and sent to you for you to review with your client.
- Generally, clients will not receive any results from CCVS.



NOTICE

CE CREDIT CERTIFICATES & PRESENTATION SLIDES WILL BE EMAILED TO YOU.
IF YOU DO NOT RECEIVE AN EMAIL WITH THIS INFORMATION WITHIN A WEEK, CONTACT NICHOLE -
NICHOLEMANFREDI@CAPECODVETSPECIALISTS.COM

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