# Current Concepts in Canine Biliary Tract Disease

VMA NYC-10/6/2021

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MICHIGAN STATE UNIVERSITY VETERINARY MEDICAL CENTER

*Special thanks to David C Twedt

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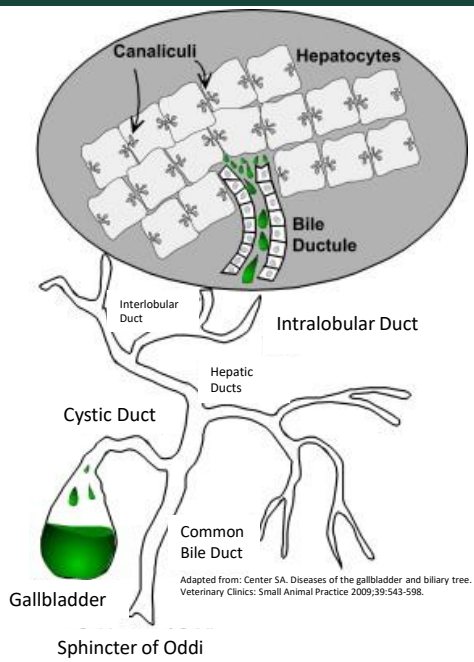
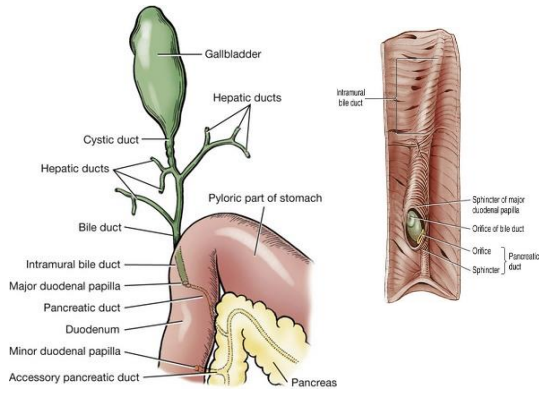



Adapted from: Center SA. Diseases of the gallbladder and biliary tree. Veterinary Clinics: Small Animal Practice 2009;39:543-598.




From: Evans HE, de Lahunta A: Miller's anatomy of the dog, Ed. 4 2013. Elsevier, St. Louis.

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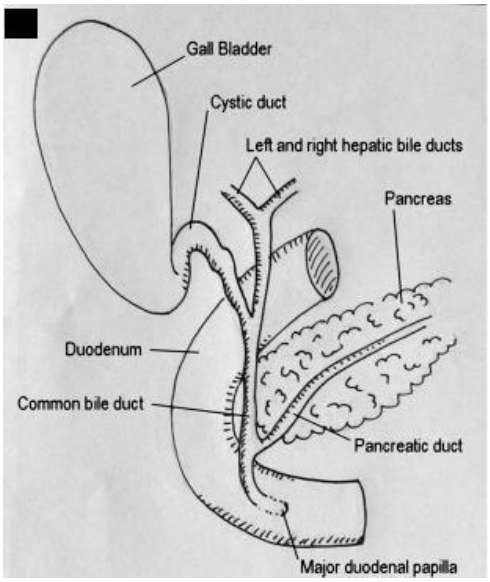
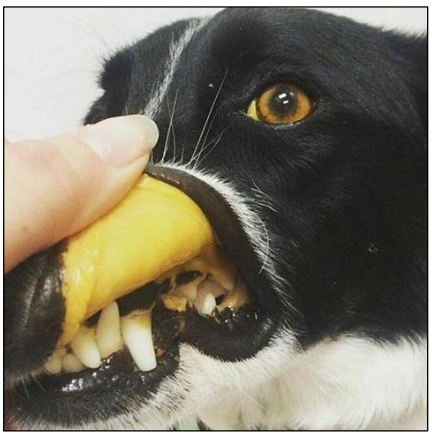



From: Best EJ, et al. Suspected choledochal cyst in a domestic shorthair cat. JFMS 2010; 12:814-817,

3

# Clinical signs & PE

- Acute vs. chronic progressive vs. chronic intermittent
- Non-specific or specific
- Severe or subtle (pain)



- Physical exam
  - Poor body condition
  - Jaundice
  - Hepatomegaly
  - Abdominal pain
  - Elevated body temp
  - Acholic feces

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# General laboratory findings

- Hypercholesterolemia
- Increased serum alkaline phosphatase (ALP)
- Increased serum gamma glutamyltransferase (GGT)
- +/- increase serum alanine aminotransferase (ALT)
- +/- hyperbilirubinemia

- In severe cases:
- Hypotension, may be severe
- Vitamin deficiencies
  - Fat malabsorption
  - Bleeding tendencies (vitamin K)

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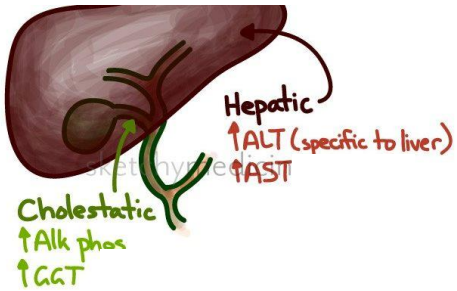
# Elevated alkaline phosphatase

- Differentials
  - Age
  - Breed-related disorders (Siberian husky)
  - Drug-induced
  - Bone-related disorders
  - Chronic stress or acute phase response
  - Hyperadrenocorticism
  - Primary hepatobiliary disease
  - Extra-hepatic disease resulting in cholestasis (pancreatitis, severe duodenitis, pancreatic or duodenal neoplasia)
  - Systemic disorders resulting in cholestasis

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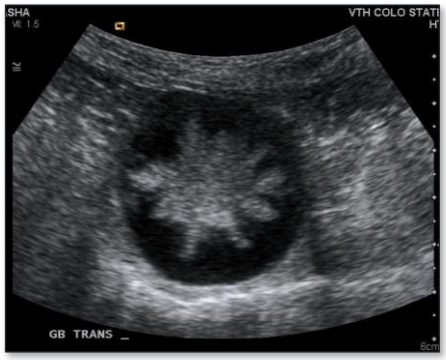
# Imaging

- Plain radiography
- Abdominal ultrasound
  - Long considered imaging modality of choice
  - Limitations

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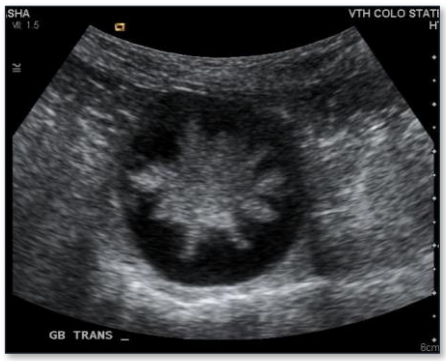
# Imaging

**Evaluation of contrast-enhanced ultrasonography as a method for detecting gallbladder necrosis or rupture in dogs**

P Bargellini, R Orlandi, C Paloni, G Rubini, P Fonti, ME Peterson, M Rishniw, C Boiti
*Vet Radiol Ultrasound 2016;57:611-620*

- *93 dogs with GB lesions identified via traditional AUS*
- *CEUS: gas-filled microbubbles administered IV; real-time perfusion images of target organs*
- *Sulfur-hexafluoride echo-signal enhancer (0.03ml/kg IV cephalic catheter)*
- *CEUS 100% sensitive and specific for GB rupture/necrosis*
- *Traditional AUS 75% sensitive and 81% specific*

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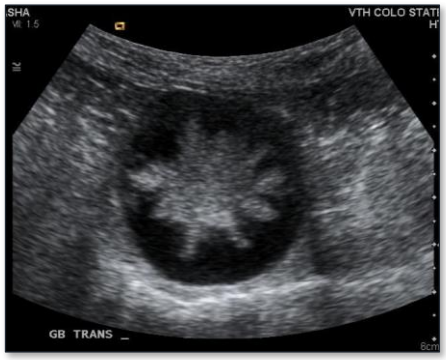
# Imaging

**Gallbladder mucocele: variables associated with outcome and the utility of ultrasonography to identify gallbladder rupture in 219 dogs (2007-2016)**

JA Jaffey, A Graham, E VanEerde, E Hostnik, W Alvarez, J Arango, C Jacobs, AE DeClue
*J Vet Intern Med 2018;32:195-200*

- *Multicenter, 219 dogs with GBM*
- *AUS for GB rupture*
  - *56.1% sensitive*
  - *91.7% specific*

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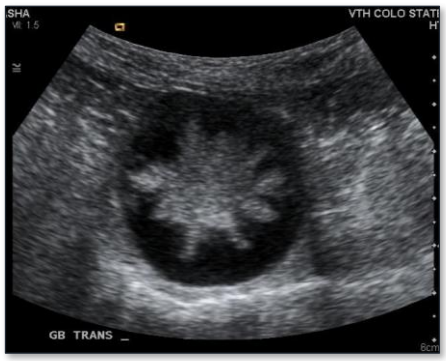
# Imaging

**Association between gallbladder ultrasound findings and bacterial culture of bile in 70 cats and 202 dogs**

R Policelli Smith, JL Gookin, W Smolski, MF Di Cicco, M Correa, GS Seiler
*J Vet Intern Med 2017;31:1451-1458*

- *AUS high sensitivity in cats (96%), low specificity(49%)*
- *AUS 81% sensitive and 31% specific in dogs*
- *No US abnormalities were associated with positive bacterial culture in the dog*

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# Imaging

- MRI
- CT
- CT cholangiography

Diagnostic Imaging of the Hepatobiliary System
An Update

Angela J. Marolf, DVM

KEYWORDS
• Computed tomography • CT • Magnetic resonance imaging • MRI
• Contrast-enhanced ultrasound • Elastography • Liver • Biliary

KEY POINTS
• Computed tomography (CT) and MRI are useful in the evaluation of liver and biliary tract disorders.
• The use of intravenous contrast with CT and MRI provides additional information that can aid in distinguishing different disease processes.
• The lack of superimposition of adjacent stomach and bowel gas, as well as decreased operator dependence of these imaging modalities, leads to more accurate assessments of the cranial abdomen.
• Advanced techniques in ultrasound of the hepatobiliary system may be useful in the evaluation of liver and biliary tract disorders.

INTRODUCTION

Abdominal radiography and ultrasound have been performed in dogs and cats for evaluation of liver and biliary abnormalities for many years in veterinary medicine. Abdominal ultrasound, in particular, has been used for diagnosis of biliary tract and parenchymal liver diseases. Ultrasound imaging is very sensitive at identifying liver and biliary abnormalities but often lacks specificity, and cytology or histology are required for definitive diagnosis. Advantages to abdominal ultrasound include the ability to perform the study on awake or sedated patients, use of nonionizing sound waves, and the ability of ultrasound to distinguish fluid and soft tissue changes. Disadvantages to sonographically evaluating the liver and biliary system include similarity in the appearance of different disease processes, incomplete assessment of the organs due to deep-chested body conformation or overlying stomach and bowel gas,

Disclosure Statement: The author has nothing to disclose.
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0195-5616/17/© 2016 Elsevier Inc. All rights reserved.

Computed Tomography and MRI of the Hepatobiliary System and Pancreas

Angela J. Marolf, DVM

KEYWORDS
• Computed tomography • MRI • Liver • Biliary system • Pancreas

KEY POINTS
• CT and MRI are useful in the evaluation of liver, biliary tract, and pancreatic disorders.
• The use of intravenous contrast provides additional information that can aid in distinguishing different disease processes.
• The lack of superimposition of adjacent stomach and bowel gas and decreased operator dependence of these imaging modalities leads to more accurate assessments of the cranial abdomen.

INTRODUCTION

Abdominal radiography and ultrasound have been performed in dogs and cats for evaluation of liver, biliary, and pancreatic abnormalities for many years in veterinary medicine. Abdominal ultrasound in particular has been used for diagnosis of biliary, pancreatic, and parenchymal liver diseases. Advantages to abdominal ultrasound include ability to perform the study on awake or sedated patients, use of nonionizing sound waves, and the ability of ultrasound to distinguish fluid and soft tissue changes. Disadvantages to sonographically evaluating the hepatobiliary system and pancreas include incomplete assessment of the organs because of overlying stomach and bowel gas that interferes with the ultrasound wave propagation and patient discomfort or poor compliance during the study. Additionally, ultrasound is highly operator dependent, and thorough evaluation of these organs is limited by experience level of the sonographer.

Disclosure statement: The author has nothing to disclose.
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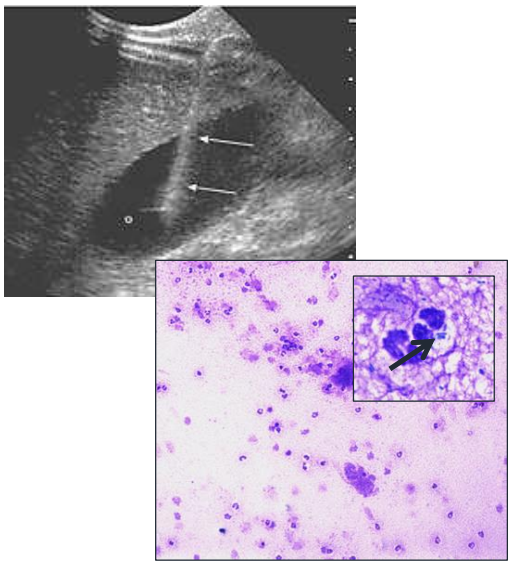
Percutaneous ultrasound-guided cholecystocentesis (PUC)

**Association between gallbladder ultrasound findings and bacterial culture of bile in 70 cats and 202 dogs**

R Policelli Smith, JL Gookin, W Smolski, MF Di Cicco, M Correa, GS Seiler
*J Vet Intern Med 2017;31:1451-1458*

- *Complications 7/208 PUC events dogs; 2/72 PUC events cats*
  - *Most common small amount peritoneal hemorrhage*
  - *No fatal complications*



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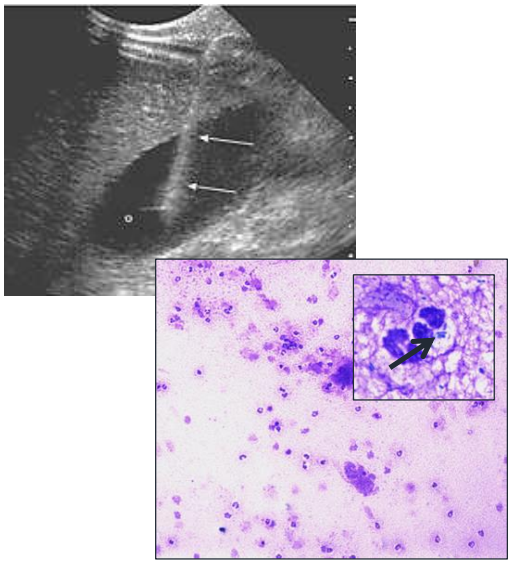
## Percutaneous ultrasound-guided cholecystocentesis (PUC)

**Percutaneous ultrasound-guided cholecystocentesis: complications and association of ultrasonographic findings with bile culture results**

F Schiborra, JF McConnell, TW Maddox
*J Sm Anim Pract 2017;58:389-384*

- *Complications 8/300 cholecystocentesis events – 5 dogs and 3 cats*
  - *Bile peritonitis 2 dogs (GBM and septic cholecystitis)*
  - *3 patients cardiopulmonary arrest (2 cats, 1 dog [under anesthesia])*



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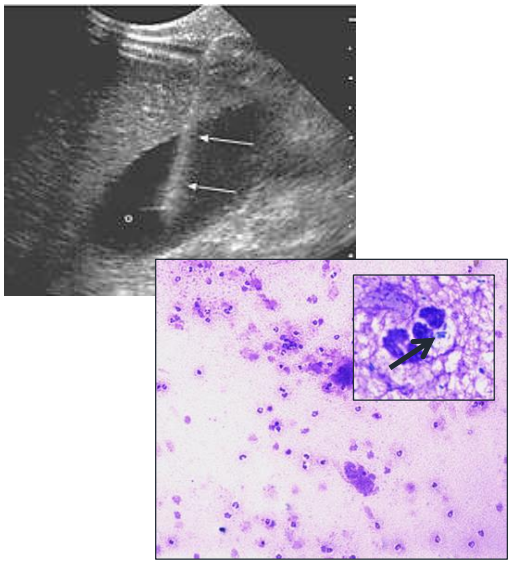
## Percutaneous ultrasound-guided cholecystocentesis (PUC)

**Cytologic findings in 140 bile samples from dogs and cats and associated clinical pathological data**

LM Peters, B Glanemann, OA Garden, B Szladovits
*J Vet Intern Med 2016;30:123-131*

- *Complications 4 dogs, 1 cat*
  - *Bile peritonitis in 2 dogs*
    - *neuroendocrine carcinoma of pancreas, duodenum and liver*
    - *GB intact- LP cholecystitis and pancreatitis*



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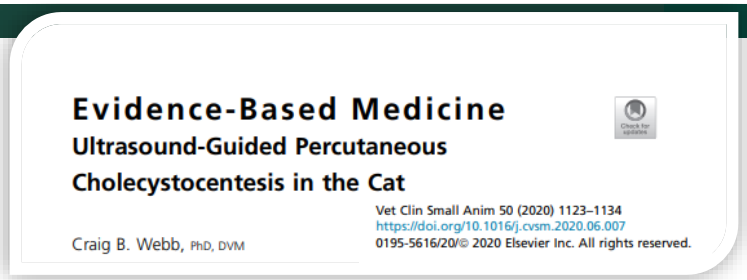

**Evidence-Based Medicine**

**Ultrasound-Guided Percutaneous Cholecystocentesis in the Cat**

Craig B. Webb, PhD, DVM

Vet Clin Small Anim 50 (2020) 1123–1134
https://doi.org/10.1016/j.cvsm.2020.06.007


Summary:

- "The literature shows that PUC is performed safely with few reported complications."
- "When performed carefully following thoughtful case selection, the evidence supports the use of PUC as a safe was to obtain samples of bile for cytology and culture, results that may impact the diagnosis and treatment recommendations in this patient population."

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# Therapy

- Identification and treatment of underlying disorder
- Cholecystectomy or other surgical intervention? Biopsy the liver!
- Infection

| Isolate | # of cases |
|---|---|
| Escherichia coli | 6 |
| Enterococcus spp. | 5 |
| Campylobacter jejuni | 1 |
| Bacillus licheniformis | 1 |
| Clostridium perfringens | 1 |
| Proteus sp. | 1 |
| Staphylococcus sp. (coagulase neg) | 1 |

Peters LM, et al. Cytological findings of 140 bile samples from dogs and cats and associated clinical pathological data. J Vet Intern Med 2016;30:123–131.

| Isolate | # of cases |
|---|---|
| Escherichia coli | 17 |
| Enterococcus spp. | 8 |
| Clostridium spp. | 5 |
| Enterobacter cloacae | 1 |
| Klebsiella sp. | 1 |
| Proteus sp. | 1 |
| Bacteroides sp. | 1 |

Tamborini A, et al. Bacterial cholangitis, cholecystitis, or both in dogs. J Vet Intern Med 2016;30:1046–1055

| Isolate | # of cases |
|---|---|
| Escherichia coli | 6 |
| Enterococcus spp. | 5 |
| Enterobacter sp. | 1 |
| Bacteriodes fragilis | 1 |
| Clostridium perfringens | 1 |

Lawrence YA,, et al. Characterization, treatment, and outcome of bacterial cholecystitis and bactibilia in dogs. J Am Vet Med Assoc 2015;246:982–989.

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**Table 1.** Identities and prevalence of bacteria isolated by culture of bile from dogs and cats with suspected bacterial cholangitis

| Bacterial Identity | Number (%) of Bacterial Cultures | | | | |
|---|---|---|---|---|---|
| | Total | Canine | Feline | Pure | Mixed |
| Positive bile culture | 65/280 (23%) | 40/208 (19%) | 25/72 (35%) | 49/65 (75%) | 16/65 (25%) |
| *Escherichia coli* | 32/65 (49%) | 18/40 (45%) | 14/25 (56%) | 19/32 (59%) | 13/32 (41%) |
| *Enterococcus* spp. | 25/65 (38%) | 15/40 (37.5%) | 10/25 (40%) | 13/25 (52%) | 12/25 (48%) |
| *E. faecium* | 13 | 8 | 5 | 7 | 6 |
| *E. faecalis* | 6 | 5 | 1 | 4 | 2 |
| *E. casseliflavus* | 2 | 0 | 2 | 1 | 1 |
| *E. gallinarum* | 2 | 0 | 2 | 0 | 2 |
| *Enterococcus* sp. | 2 | 2 | 0 | 1 | 1 |
| *Streptococcus* spp. | 6/65 (9%) | 4/40 (10%) | 2/25 (8%) | 4/6 (67%) | 2/6 (33%) |
| *Strep. sp. (Group G)* | 3 | 1 | 2 | 1 | 2 |
| *Strep. anginosus* | 1 | 1 | 0 | 1 | 0 |
| *Strep. bovis* | 1 | 1 | 0 | 1 | 0 |
| *Strep. mutans* | 1 | 1 | 0 | 1 | 0 |
| *Staphylococcus* spp. | 5/65 (8%) | 4/40 (10%) | 1/25 (4%) | 5/5 (100%) | 0/5 (0%) |
| *Staph. epidermidis* | 2 | 1 | 1 | 2 | 0 |
| *Staphylococcus* sp. | 3 | 3 | 0 | 3 | 0 |
| *Clostridium* sp. | 3/65 (5%) | 2/40 (5%) | 1/25 (4%) | 3/3 | 0/3 |
| *Corynebacterium* sp. | 2/65 | 2/40 | 0/25 | 2/2 | 0/2 |

Policelli Smith R, Association between gallbladder ultrasound findings and bacterial culture of bile in 70 cats and 202 dogs. J Vet Intern Med. 2017;31:1451-1458.

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## Selected hepatosupportive medications in the treatment of cholestatic hepatopathies

| Agent | Mechanisms of Action | Dosing | Side Effects |
|---|---|---|---|
| S-adenosylmethione | Anti-apoptotic<br>Antioxidant: increases glutathione<br>Modulates cytokine expression | 20 mg/kg/d, PO (best administered in fasted state) | None |
| Ursodeoxycholic acid | Choleretic<br>Anti-apoptotic<br>Immunomodulatory<br>Replacement of hepatotoxic bile acids | 10-15 mg/kg/d, PO (best given with food)<br><br>*Can increase dose to 20-30 mg/kg/d (divided q 12 h) with severe cholestasis | Vomiting (rare)<br><br>*may increase bioavailability of cyclosporine |
| Silymarin | Antifibrotic<br>Choleretic<br>Anti-inflammatory<br>ROS scavenger | Silymarin: 20-50 mg/kg/d (divided q 6-8 h, PO)<br><br>Siliphos: 3-6 mg/kg/d, PO | None |
| Vitamin E | Anti-oxidant<br>Anti-inflammatory | 10-15 IU/kg/d,PO (alpha-tocopherol acetate) | None at recommended doses |

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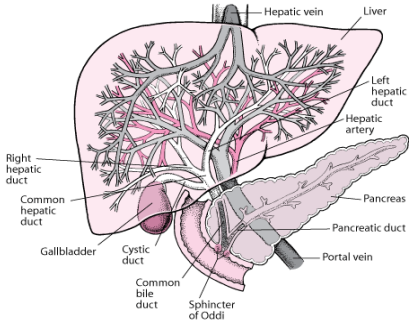
# Categories of biliary tract disease

- Cholestasis
- Disease of the gallbladder
  - Gallbladder mucocele (GBM)
  - Cholecystitis
- Cholangitis
- Congenital disease of the biliary tract
  - Congenital hepatic fibrosis/juvenile polycystic disease
  - Caroli's disease/congenital dilation of the large and segmental bile ducts

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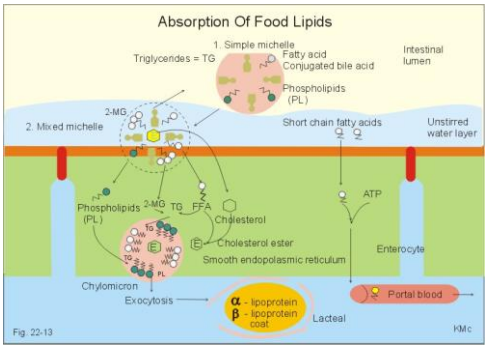
# Cholestasis

- Causes: GBM, cholangitis, extrahepatic bile duct obstruction (EHBDO), chronic hepatitis, and extrahepatic infection and inflammation

- Consequences of cholestasis
  - Disrupts conjugation of BA
  - Hepatic retention of compounds
  - Changes the gut microbiome
  - Alters intestinal permeability
  - Fat malabsorption




PE Paulev, G Zubieta-Calleja. Human Physiology. Ed. 2 Copenhagen.

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## Cholestasis of inflammation/infection

**Cholestasis associated with extrahepatic bacterial infection in five dogs**

*J Taboada, DJ Meyer*
*J Vet Intern Med 1989; 3:216-221*

- *Mechanism poorly understood*
- *Acute phase reactants interfere with hepatocyte binding bile salts*
- *Endotoxins interfere with Na+, K+, ATPase pumps*

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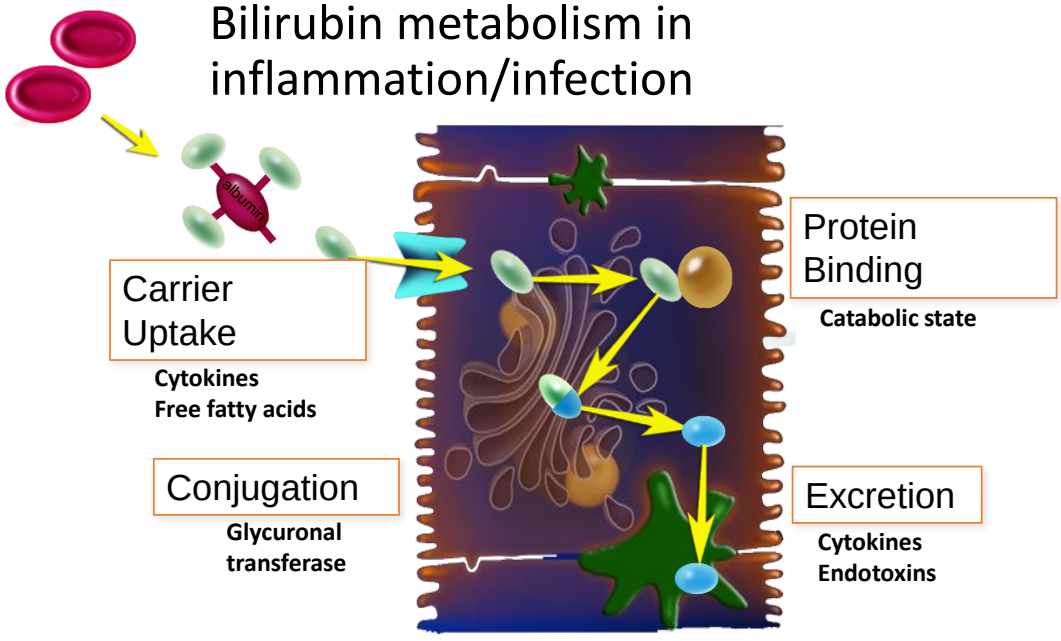
## Bilirubin metabolism in inflammation/infection

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# Specific Canine Biliary Tract Disorders

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## Gallbladder Mucocele (GBM)

- Common and clinically important cause of extrahepatic biliary disease in the dog
- Characterized by the accumulation of viscoud bile and mucus in the GB, and cystic mucinous hyperplasia histologically
- Underlying cause not well understood
  - May involve excess secretion of gel-forming mucins
  - May involve GB dysmotility

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## GBM- breeds






**Gallbladder mucoceles in Border terriers**
F Allerton, et al. ; J Vet Intern Med 2018; 32:1618-1628
◆Odds of identifying GBM in BT 85x that of other breeds

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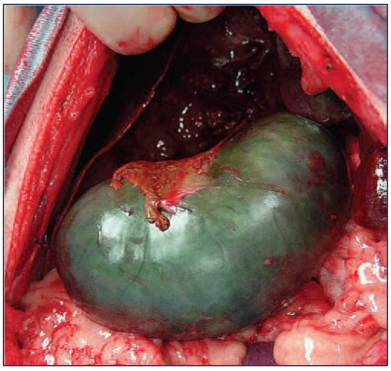
## Risk factors GBM



- Hypothyroidism
- Hyperadrenocorticism
- Hyperlipidemia
- GB dysmotility
- Glucocorticoid usage?
- Imidicloprid in Shetland sheepdogs

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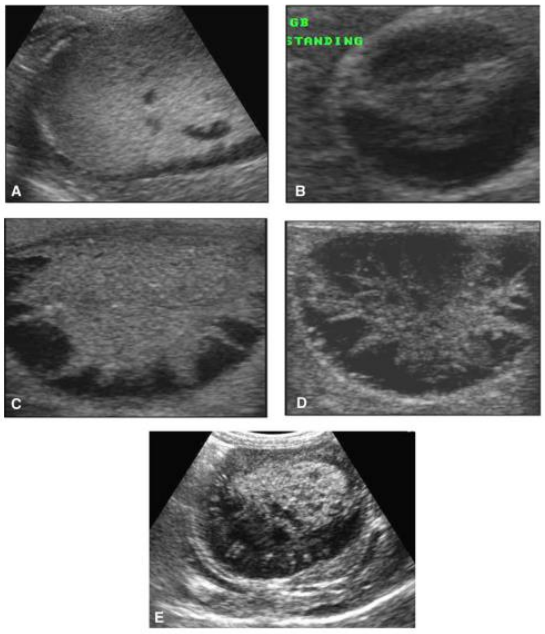
# Imaging- GBM

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(A) Type 1-echogenic immobile bile occupying the gallbladder.
(B) Type 2- an incomplete stellate pattern
(C) Type 3- a typical stellate pattern
(D) Type 4-a kiwi fruit-like pattern and stellate combination
(E) Type 5 -kiwi fruit-like pattern with residual central echogenic bile.

COMPARISON BETWEEN ULTRASONOGRAPHIC AND CLINICAL FINDINGS IN 43 DOGS WITH GALLBLADDER MUCOCELES

JIHYE CHOI, AHYOUNG KIM, SEOYEON KEH, JUYEON OH, HYUNWOOK KIM, JUNGHEE YOON

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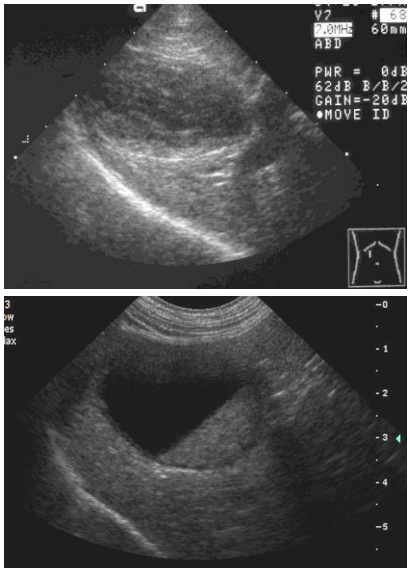
# Biliary sludge

**Spontaneous course of biliary sludge over 12 months in dogs with ultrasonographically identified biliary sludge**

SM DeMonaco, DC Grant, MM Larson, DL Panciera, MS Leib
*J Vet Intern Med 2016;30:771-778*

- *77 healthy client-owned dogs screened, 45 sludge*
- *No significant change in degree of sludge over 12 months*
- *No significant change in gravity-dependency over 12 months*
- *24% of dogs with gravity dependent sludge developed a combination of non-dependent and dependent sludge*

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# GBM- concurrent disease

PAPER

## Eubacterial fluorescence *in situ* hybridisation and histologic features in 25 dogs with gallbladder mucocele

S. A. Wennogle[1,*], E. K. Randall[†], S. L. Priestnall[‡], D. C. Twedt[*] and K. W. Simpson[§]

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[§]College of Veterinary Medicine, Cornell University, Ithaca, New York 14853 USA

[1]Corresponding author email: sara.wennogle@colostate.edu

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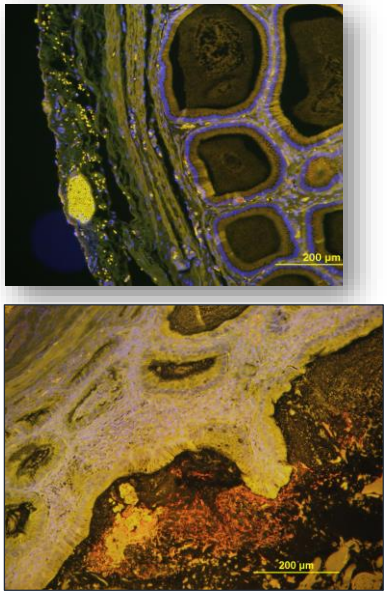
## GBM- concurrent disease

- Bacterial infection
  - 3-67% of cases
  - 25 cases of GBM
    - 8/25 (32%) FISH +
      - Bacteria adherent/invasive GB epithelium
    - 1/8 dogs + bacterial culture

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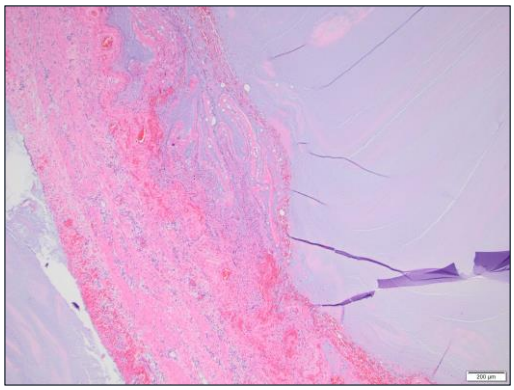
## GBM- concurrent disease

- Cholecystitis
  - 17-40%
  - 25 cases of GBM
    - 68% had cholecystitis
    - Mild 47%
    - Moderate-severe 53%
- Cholangitis/ Cholangiohepatitis?



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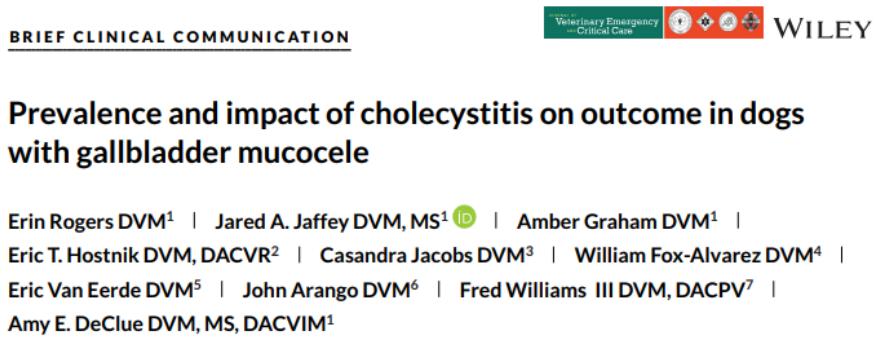
# Cholecystitis or cholangitis/cholangiohepatitis outcome?



BRIEF CLINICAL COMMUNICATION

Veterinary Emergency and Critical Care WILEY

**Prevalence and impact of cholecystitis on outcome in dogs with gallbladder mucocele**

Erin Rogers DVM[1] | Jared A. Jaffey DVM, MS[1] | Amber Graham DVM[1] | Eric T. Hostnik DVM, DACVR[2] | Casandra Jacobs DVM[3] | William Fox-Alvarez DVM[4] | Eric Van Eerde DVM[5] | John Arango DVM[6] | Fred Williams III DVM, DACPV[7] | Amy E. DeClue DVM, MS, DACVIM[1]

- Presence of cholecystitis not associated with short-term survival in 219 dogs that underwent cholecystectomy for treatment of GBM

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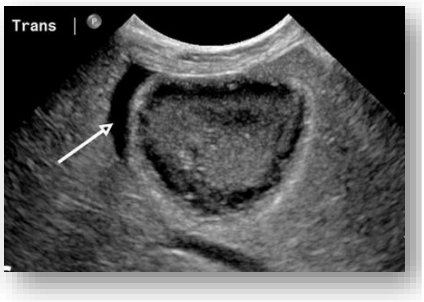
# Cholecystitis or cholangitis/cholangiohepatitis and long-term outcome?

- Not well understood, we are currently evaluating this in 74 dogs with GBM
  - 55/74 (73%) had cholecystitis
  - 35/74 (47%) had portal inflammation
  - 14/74 (19%) had cholangitis
  - 9/74 (12%) had cholangiohepatitis
  - 28/74 (38%) had other hepatitis (centrilobular, random)
  - 21/74 (28%) had hepatic fibrosis

34

# GBM- concurrent disease




Extra-hepatic biliary tract obstruction (EHBDO) (25%)

Rupture (23-61%)

- AUS – discontinous GB wall, peri-GB fluid, peritoneal effusion, hyperechoic fat
- Neutrophilia left shift, higher serum ALT,ALP, bilirubin

35

# GBM- Rupture

**Dogs with biliary rupture based on ultrasound findings may have normal total serum bilirubin values**

Kassandra Wilson[1] | Danielle Powers[1] | Britton Grasperge[2] | Chin-Chi Liu[1] | L. Abbigail Granger[1]

*Vet Radiol Ultrasound.* 2021;62:236–245.

- 12/30 (40%) of dogs with confirmed ruptured biliary tracts had a serum bilirubin concentrations within the normal reference range
- No statistical difference was found in serum bilirubin values between ruptured and nonruptured biliary tracts.

36

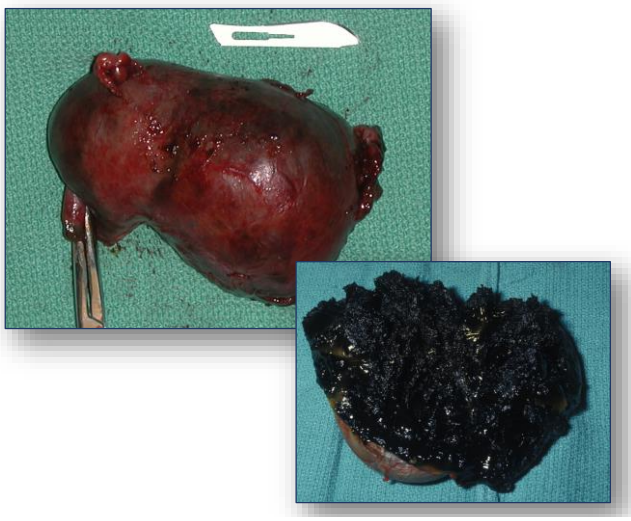
## GBM- therapeutic decisions

- *Symptomatic
- *Asymptomatic with abnormal serum biochemistry
- *Asymptomatic with normal serum biochemistry

37

## GBM- therapeutic decisions

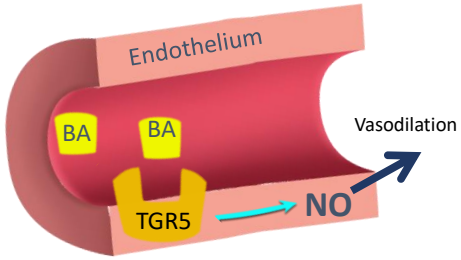
- *Symptomatic
- *Asymptomatic with abnormal serum biochemistry



38

## GBM-cholecystectomy

- 27% risk of mortality within 2 weeks of surgery
- Dogs with GB rupture 2.7x more likely to die
- Refractory hypotension
  - Endotoxemia
  - Vasodilatory actions of bile acids
  - Vagal effects from manipulation of biliary tract
  - Relative adrenal insufficiency




39

## GBM-cholecystectomy

- NON-ELECTIVE VS ELECTIVE

**Outcome of elective cholecystectomy for treatment of gallbladder disease in dogs**

*G Youn, MJ Waschak, KAR Kunkel, PD Gerard*
*J Am Vet Med Assoc 2018;252:970-975*

- *45 dogs having elective surgery; 2% mortality*
- *24 dogs having non-elective (icterus & suspect EHBDO or rupture) surgery; 20% mortality*

40

## GBM- Surgery

- Liver biopsy at time of surgery

**Gallbladder mucocele in dogs: 30 cases (2000-2002)**

*FS Pike, J Berg, NW King, DG Penninck, C Webster*
*J Am Vet Med Assoc 2004;224:1615-1622*

- *12 dogs had serial examinations*
  - *9 dogs persistent LE elevations*
  - *6 dogs had persistent hepatic AUS abnormalities*

41

## GBM- Surgery

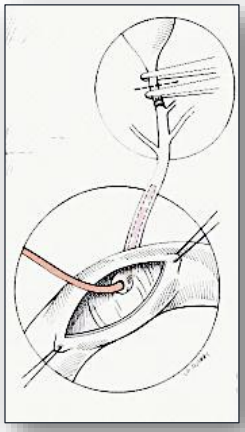
**Clinical findings and prognostic factors for dogs undergoing cholecystectomy for gallbladder mucocele**

*S Malek, E Sinclair, G Hosgood, NMM Moens, T Baily, SE Boston*
*Vet Surg 2013;42:418-426*

- *94.4% of dogs had abnormalities on liver biopsy*
- *8 dogs died within 2 weeks*
- *3 dogs died of complications from liver disease within 19 months*

42

## GBM- Surgery



EHBDO

Post-operative therapies

- Treat concurrent diseases
- Low fat diet
- Ursodeoxycholic acid
- S-adenosylmethione

43

## GBM-Medical therapy

Asymptomatic with normal serum biochemistry

Cholecystectomy declined

Therapy

- Treat underlying disease
- Low fat diet
- Ursodeoxycholic acid
- S-adenosylmethione
- +/- broad spectrum antibiotics

- Therapeutic failure definition?

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# GBM- Medical vs surgical management?

STANDARD ARTICLE

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

**Long-term survival of dogs treated for gallbladder mucocele by cholecystectomy, medical management, or both**

Max Parkanzky[1] | Janet Grimes[1] | Chad Schmiedt[1] | Scott Secrest[2] | Andrew Bugbee[1]

- Longer survival times were seen with surgical management vs. medical management (median 1802 days vs. 1340 days)
- Dogs who received medical followed by surgical outcome had worst survival times (median 203 days)

45

# GBM- therapeutic decisions

- *Asymptomatic with normal serum biochemistry

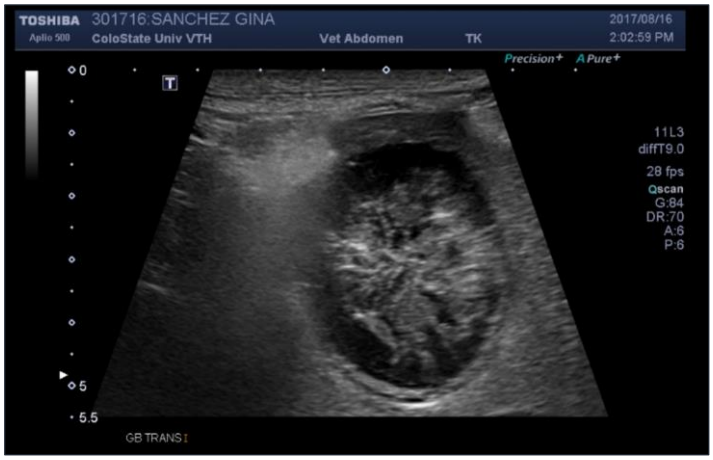
Gina 11-year-old FS Australian shepherd mix

- Historically hypothyroid (controlled)
- Wellness exam

46

# Gina

August 2017- not eating, vomiting




August 2017

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| Tech 1 Comments: | Grossly Hemolyzed | |
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| GLUCOSE | 114 | |
| BUN | 9 | |
| CREATININE | 0.3 | L |
| PHOSPHORUS | 4.5 | |
| CALCIUM | 8.7 | L |
| MAGNESIUM | 2.1 | |
| TOTAL PROTEIN | 6.0 | |
| ALBUMIN | 3.0 | |
| GLOBULIN | 3.0 | |
| A/G RATIO | 1.0 | |
| CHOLESTEROL | 485 | H |
| T-BILIRUBIN | 4.4 | H |
| ALP | 2324 | H |
| ALT | 1039 | H |
| AST | 272 | H |
| CK | 253 | |
| GGT | 9 | |
| SODIUM | 141 | L |
| POTASSIUM | 3.50 | L |
| CHLORIDE | 99.3 | L |
| BICARBONATE (HCO3-) | 21.0 | |
| ANION GAP | 24 | H |
| CALCULATED OSMOLALITY | 278 | |
| IRON | 56 | L |
| HEMOLYSIS | 401 | H |
| ICTERUS | 5 | H |
| LIPEMIA | 10 | |

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# Gina

*DIAGNOSES:*
*1. Gallbladder: Biliary mucocele with mild suppurative capsulitis.*
*2. Liver: Moderate, subacute, suppurative, cholangiohepatitis*

**Chemistry**

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| Tech 1: | CLP | TLW | JMJ | CLP | TLW | |
| Tech 1 Comments: | | Hemolyzed, lipemic. | | | | |
| GLUCOSE | 102 | 112 | 104 | 91 | 110 | 70 - 115 mG/dL |
| BUN | 28 | 20 | 14 | 13 | 9 | 7 - 30 mG/dL |
| CREATININE | 0.8 | 0.8 | 0.6 | 0.6 | 0.3 L | 0.6 - 1.6 mG/dL |
| PHOSPHORUS | 5.2 | 4.9 | 5.1 | 5.7 | 3.4 | 2.5 - 6.0 mG/dL |
| CALCIUM | 10.3 | 10.5 | 10.3 | 9.8 | 8.2 L | 9.0 - 11.5 mG/dL |
| MAGNESIUM | 2.1 | 1.9 | 1.7 L | 1.9 | 2.0 | 1.8 - 2.4 mG/dL |
| TOTAL PROTEIN | 5.9 | 5.5 | 6.0 | 5.2 | 4.6 L | 5.0 - 7.0 G/dl |
| ALBUMIN | 3.7 | 3.4 | 3.5 | 3.1 | 2.3 L | 3.0 - 4.3 G/dl |
| GLOBULIN | 2.2 | 2.1 | 2.5 | 2.1 | 2.3 | 1.5 - 3.2 G/dl |
| A/G RATIO | 1.7 | 1.6 | 1.4 | 1.5 | 1.0 | 0.9 - 2.4 RATIO |
| CHOLESTEROL | 163 | 180 | 267 | 230 | 395 H | 130 - 300 mG/dL |
| T-BILIRUBIN | 0.0 | 0.0 | 0.1 | 0.2 | 1.0 H | 0.0 - 0.2 mG/dL |
| ALP | 39 | 69 | 267 H | 743 H | 2991 H | 15 - 140 IU/L |
| ALT | 30 | 46 | 95 H | 143 H | 606 H | 10 - 90 IU/L |
| AST | 24 | 25 | 27 | 28 | 52 H | 15 - 45 IU/L |
| CK | 110 | 113 | 114 | 178 | 222 | 50 - 275 IU/L |
| GGT | 0 | 0 | 7 | 8 | 21 H | 0 - 9 IU/L |
| SODIUM | 149 | 152 | 148 | 145 | 147 | 142 - 152 mEQ/L |
| POTASSIUM | 4.81 | 5.20 | 5.18 | 5.32 | 3.89 L | 3.9 - 5.4 mEQ/L |
| CHLORIDE | 112.4 | 110.6 | 107.9 L | 110.0 | 113.0 | 108 - 118 mEQ/L |
| BICARBONATE (HCO3-) | 23.7 | 26.4 H | 22.0 | 20.0 | 18.0 | 15 - 25 mEQ/L |
| ANION GAP | 18 | 20 | 23 | 20 | 20 | 12 - 23 mmol/L |
| CALCULATED OSMOLALITY | 302 | 306 | 296 | 289 | 290 | mOsm/Kg |
| IRON | 137 | 193 | 127 | 95 | 52 L | 80 - 270 uG/dL |
| HEMOLYSIS | 59 | 103 H | 21 | 40 | 1 | 0 - 100 mG/dL |
| ICTERUS | 0 | 0 | 0 | 0 | 1 | 0 - 1 mG/dL |
| LIPEMIA | 44 | 107 H | 17 | 1 | 11 | 0 - 80 mG/dL |

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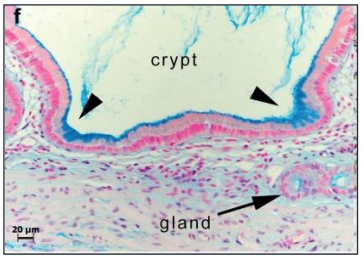
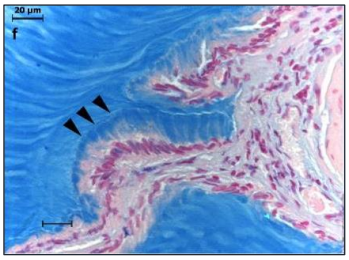
# Food for thought/Future directions GBM

RESEARCH ARTICLE

## Excess Secretion of Gel-Forming Mucins and Associated Innate Defense Proteins with Defective Mucin Un-Packaging Underpin Gallbladder Mucocele Formation in Dogs

Mehmet Kesimer[1], John Cullen[2], Rui Cao[1], Giorgia Radicioni[1], Kyle G. Mathews[3], Gabriela Seiler[4], Jody L. Gookin[3]*




- Significant increase in Muc5ac
  - promotes a more cross-linked, viscous and rubber-like mucus
- Increased FCGBP and TFFIII: mucin cross-linkers
  - alter the physical and functional properties of the mucus

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RESEARCH ARTICLE

## Qualitative metabolomics profiling of serum and bile from dogs with gallbladder mucocele formation

Jody L. Gookin[1]*, Kyle G. Mathews[1], John Cullen[2], Gabriela Seiler[3]

PLOS ONE

| Metabolite | Location | Fold Change | P-value | Description |
|---|---|---|---|---|
| Taurine | Bile | -20.0 | 0.000077 | Predominant amino acid used for conjugation of bile acids. Modulator of CYP7A1 activity. |
| Ascorbate | Bile | -16.7 | 0.0018 | Vitamin C. Anti-oxidant. Biological regulator of CFTR-mediated $Cl^-$ secretion. |
| Nicotinamide riboside | Bile | -10.0 | 0.0111 | Precursor for synthesis of coenzymes NAD and NADP needed for energy-producing redox reactions. |
| Dihydrobiopterin | Bile | -5.0 | 0.0006 | Precursor of tetrahydrobiopterin which is a required cofactor for conversion of aromatic amino acids to monoamine neurotransmitters and for synthesis of nitric oxide. |
| Riboflavin | Bile | -5.0 | 0.0066 | Vitamin B2. Coenzyme required for synthesis of flavin nucleotides FMN and FAD. |
| Pantothenate | Bile | -3.2 | 0.0021 | Vitamin B5. Precursor needed for synthesis of coenzyme A (CoA). |
| Adenosine | Serum | -16.7 | 0.0063 | Extracellular signaling molecule. Activates purinergic receptors to stimulate CFTR-mediated $Cl^-$ secretion. |
| Deoxycarnitine | Serum | -1.37 | 0.0495 | Metabolite of carnitine. Carnitine is required for transport of fatty acids into mitochondria for β-oxidation. |

https://doi.org/10.1371/journal.pone.0191076.t005

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# GBM and proteinuria

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

**Proteinuria in dogs with gallbladder mucocele formation: A retrospective case control study**

Crystal Lindaberry[1] | Shelly Vaden[1] | Kathleen M. Aicher[1,4,5] | Gabriela Seiler[2] | James Robertson[3] | Rachel Cianciolo[4] | Ching Yang[4] | Jody L. Gookin[1]

- Found that gallbladder mucocele formation is significantly associated with proteinuria (when compared to age and breed matched controls)
- Screen your GBM patients for proteinuria
- Not sure if it resolves following of cholecystectomy

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# GBM and coagulation

STANDARD ARTICLE

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

**Evaluation of coagulation parameters in dogs with gallbladder mucoceles**

Michelle Pavlick | Armelle DeLaforcade | Dominique G. Penninck | Cynthia R. L. Webster

- 23 dogs with GBM dx by AUS (not all histopathologically confirmed)
- 19/23 dogs appeared hypercoagulable based on thromboelastographic (TEG) testing
- Traditional plasma-based coagulation testing revealed a complex state of hemostasis in GBM dogs

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## Gallbadder Mucocele- take-home points

- If found incidentally, be sure to screen for biochemical abnormalities
- In general, surgical management is preferred and best performed early/electively

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## Alex

September 2017

Alex 15 year old MC miniature schnauzer

Reduced appetite, prefers to sit down, seems confused, one episode vomiting

PE: 105.1, groans on abdominal palpation

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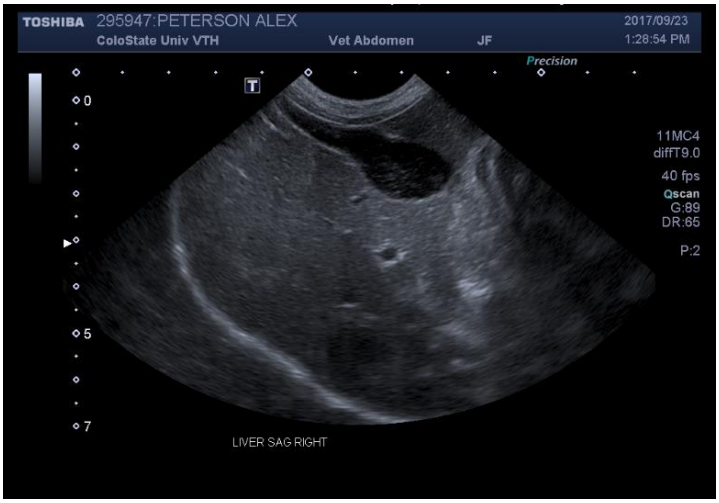
CBC:
Neut: 7.2 x 10^3/ul
Lymph: 0.9 x 10^3/ul
HCT: 35 (macrocytic, normochromic)
Retic (auto): 15.3 x 10^3/ul
PLT: 107 x10^3/ul

Biochemical profile:
ALT 713 IU/L
ALP 694 IU/L

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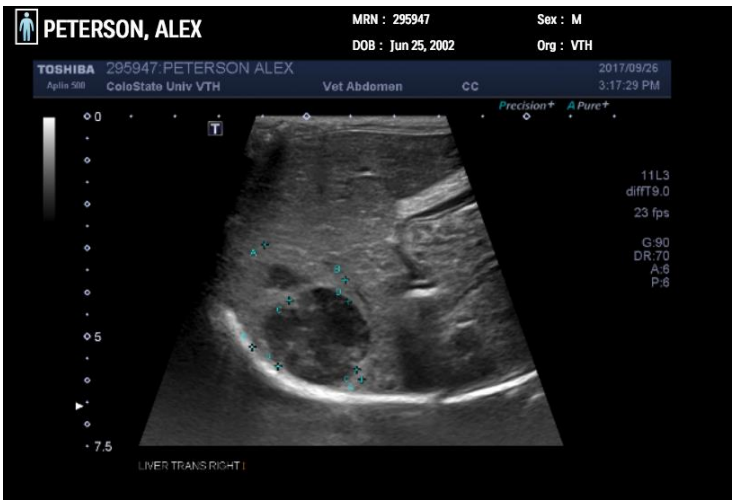


Cytology of liver mass:
Septic suppurative inflammation; large rod bacteria

Surgery:
Partial liver lobe lobectomy for abscess in quadrate lobe

Culture:
E.coli liver & bile

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Histopathology:

1)Chronic hepatic abscess with multifocal random, severe, acute neutrophilic hepatitis

2) Periportal hepatitis, mild, lymphoplasmacytic chronic with **regionally extensive portal bridging and dissecting fibrosis**, mild periportal oval cell hyperplasia, and hepatic nodular hyperplasia.

3) Acute fibrinosuppurative peritonitis

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# Alex

**Chemistry**

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| Tech 1 Comments: | | Hemolyzed, lipemic. | Hemolyzed, lipemic, ultracentrifuged. | Hemolyzed, lipemic, ultracentrifuged. | Hemolyzed, lipemic, ultracentrifuged. | |
| GLUCOSE | | | 99 | 96 | 82 | 70 - 115 mG/dL |
| BUN | | | 21 | 20 | 23 | 7 - 30 mG/dL |
| CREATININE | | | 0.6 | 0.6 | 0.8 | 0.6 - 1.6 mG/dL |
| PHOSPHORUS | | | 5.0 | 4.2 | 4.5 | 2.5 - 6.0 mG/dL |
| CALCIUM | | | 11.2 | 10.7 | 10.2 | 9.0 - 11.5 mG/dL |
| MAGNESIUM | | | 1.9 | 2.0 | 1.8 | 1.8 - 2.4 mG/dL |
| TOTAL PROTEIN | | | 6.9 | 6.7 | 6.5 | 5.0 - 7.0 G/dl |
| ALBUMIN | | | 3.8 | 3.6 | 3.0 | 3.0 - 4.3 G/dl |
| GLOBULIN | | | 3.1 | 3.1 | 3.5 H | 1.5 - 3.2 G/dl |
| A/G RATIO | | | 1.2 | 1.2 | 0.9 | 0.9 - 2.4 RATIO |
| CHOLESTEROL | | | 527 H | 338 H | 409 H | 130 - 300 mG/dL |
| T-BILIRUBIN | | | 0.1 | 0.0 | 0.3 H | 0.0 - 0.2 mG/dL |
| ALP | 1004 H | 644 H | 834 H | 711 H | 1131 H | 15 - 140 IU/L |
| ALT | 235 H | 255 H | 244 H | 198 H | 373 H | 10 - 90 IU/L |
| AST | 31 | 36 | 31 | 46 H | 56 H | 15 - 45 IU/L |
| CK | | | 278 H | 255 | 597 H | 50 - 275 IU/L |
| GGT | 10 H | 7 | 8 | 4 | 15 H | 0 - 9 IU/L |
| SODIUM | | | 147 | 146 | 150 | 142 - 152 mEQ/L |
| POTASSIUM | | | 5.18 | 6.07 H | 4.83 | 3.9 - 5.4 mEQ/L |
| CHLORIDE | | | 102.8 L | 106.6 L | 108.4 | 108 - 118 mEQ/L |
| BICARBONATE (HCO3-) | | | 23.1 | 18.5 | 18.6 | 15 - 25 mEQ/L |
| ANION GAP | | | 26 H | 27 H | 28 H | 12 - 23 mmol/L |
| CALCULATED OSMOLALITY | | | 296 | 295 L | 301 | 296 - 316 mOsm/Kg |
| IRON | | | 252 | 212 | 242 | 80 - 270 uG/dL |
| HEMOLYSIS | 78 | 145 H | 156 H | 463 H | 145 H | 0 - 100 mG/dL |
| ICTERUS | 0 | 0 | 0 | 0 | 1 | 0 - 1 mG/dL |
| LIPEMIA | 44 | 202 H | 123 H | 197 H | 109 H | 0 - 80 mG/dL |

September 2017-January 2018:

Enrofloxacin

Metronidazole

Ursodiol

Denamarin

Waxing and waning vomiting, lethargy, abnormal behavior

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# Alex

January 9 2018:

Cholecystocentesis for cytology & culture (off antibiotics):

**Cytology:**
Bactibilia cocci

**Culture:**
No aerobes
Enterococcus sp. heavy growth (MDR)

January 26 2018:
Laparoscopic cholecystectomy

Histopathology:
1. **Gallbladder:** Marked, multifocal, chronic, lymphoplasmacytic cholecystitis with mucocele
2. **Liver:** Severe, chronic portal cirrhosis

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# Alex

February 1 2018:

Waxing and waning fever since surgery

Not doing well at home

Humane euthanasia

Necropsy-
Marked peri-portal to bridging fibrosis, biliary hyperplasia, and inflammation associated with bile ducts

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| Nucleated Cells | | 17.8 | H |
| Bands | 2% | 0.4 | H |
| Neutrophils | 83% | 14.8 | H |
| Lymphocytes | 11% | 2.0 | |
| Monocytes | 4% | 0.7 | |
| Eosinophils | | 0.0 | L |
| nRBC | | | |
| Neutrophils auto | | 15.7 | |
| Plasma Protein | | 8.5 | H |
| HCT | | 31 | L |
| RBC | | 4.18 | L |
| Cell Hgb | | 10.8 | L |
| MCV | | 74 | |
| RDW | | 13.7 | |
| HGB | | 11.0 | L |
| MCHC | | 35 | |
| CHCM | | 35 | |
| Reticulocyte auto | 1% | 19.0 | |
| CH-r | | 29.2 | H |
| MCV-r | | 97 | |
| Hypochromasia | | Slight | |
| PLT | | 204 | |
| MPV | | 15.6 | H |
| Clumped Plts | | Absent | |
| Giant Plts | | | |
| Tech 1: | MJM | | |
| Tech 2: | JMJ | | |
| Pathologist: | NONE | | |

| | | |
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| Tech 1 Comments: | BUN and ALP verified. | |
| TRIGLYCERIDE | | |
| GLUCOSE | 83 | |
| BUN | 133 | HH |
| CREATININE | 3.6 | H |
| PHOSPHORUS | 12.2 | H |
| CALCIUM | 10.5 | |
| MAGNESIUM | 3.0 | H |
| TOTAL PROTEIN | 6.3 | |
| ALBUMIN | 3.0 | |
| GLOBULIN | 3.3 | H |
| A/G RATIO | 0.9 | |
| CHOLESTEROL | 386 | H |
| T-BILIRUBIN | 0.9 | H |
| ALP | 1667 | H |
| ALT | 270 | H |
| AST | 50 | H |
| CK | 320 | H |
| GGT | 11 | H |
| SODIUM | 142 | |
| POTASSIUM | 4.77 | |
| CHLORIDE | 96.7 | L |
| BICARBONATE (HCO3-) | 11.6 | L |
| ANION GAP | 38 | H |
| CALCULATED OSMOLALITY | 325 | H |
| IRON | 63 | L |
| HEMOLYSIS | 8 | |
| ICTERUS | 1 | |
| LIPEMIA | 8 | |

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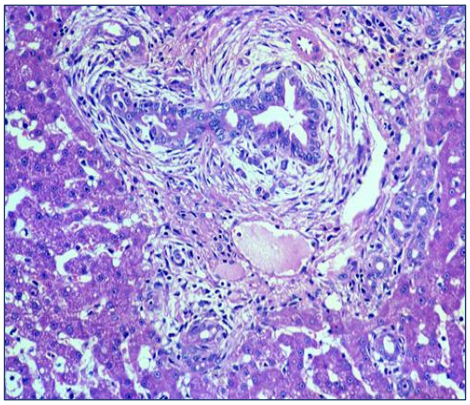
# Cholangitis

- Neutrophilic cholangitis
  - Most common
- Lymphocytic cholangitis
  - Uncommon in dog
- Destructive cholangitis
  - Loss of bile ducts
  - Drugs? Viral infxn?
  - Severe cholestasis
- Chronic cholangitis associated with liver flukes



Malek S,et al. Vet Surg.2013;42:418-26.

61

# Cholangitis

**Cholangitis and cholangiohepatitis in dogs: a descriptive study of 54 cases based on histopathological diagnosis (2004-2014)**

*JL Harrison, BJ Turek, DC Brown, C Bradley, J Callahan Clark*
*J Vet Intern Med 2018;32:172-180*

- *Middle aged; medium sized*
- *Duration of signs: 3 (0-56) days*
- *Vomiting, lethargy, inappetence, diarrhea*
- *29.6% elevated body tempterature*
- *Icterus 25.9%*

62

# Cholangitis

**Table 1.** Serum liver enzyme activity and total bilirubin and cholesterol concentrations

| Parameter | Reference Interval (RI) | Median | Range | % above RI |
|---|---|---|---|---|
| ALT (n = 49) | 16–91 U/L | 596 | 25–3,254 | 87.8 |
| AST (n = 39) | 23–65 U/L | 162 | 38–1,123 | 79.3 |
| ALP (n = 48) | 20–155 U/L | 1,506.6 | 59–8,103 | 97.9 |
| GGT (n = 29) | 7–24 U/L | 33 | 0–392 | 51.7 |
| TBILI (n = 50) | 0.1–0.5 mg/dL | 2.5 | 0.1–81 | 64.0 |
| CHOL (n = 43) | 128–317 mg/dL | 339 | 114–1,402 | 55.8 |

63

**Cholangitis and cholangiohepatitis in dogs: a descriptive study of 54 cases based on histopathological diagnosis (2004-2014)**

*JL Harrison, BJ Turek, DC Brown, C Bradley, J Callahan Clark*
*J Vet Intern Med 2018;32:172-180*

- *NC or cholangiohepatitis in 53/54 cases*
- *45/54 classified as cholangitis*
- *Most cases (77.8%) had evidence of chronicity*
- *42.6% had evidence of intrahepatic biliary obstruction*
- *Bile cultures + in 17/36 cases*

64

**Cholangitis and cholangiohepatitis in dogs: a descriptive study of 54 cases based on histopathological diagnosis (2004-2014)**

*JL Harrison, BJ Turek, DC Brown, C Bradley, J Callahan Clark*
*J Vet Intern Med 2018;32:172-180*

- *25/31 cases concurrent GB disease*
- *GB disease as a primary cause?*
- *Dogs that underwent cholecystectomy → decreased risk of death*
- *Primary disease or sequela?*

65

## Cholangitis vs. reactive hepatopathies

- Cholangitis
  - Inflammation in the **lumen and/or epithelium of bile ducts**
  - Inflammation may extend into hepatic parenchyma and result in hepatic abscess
- Reactive hepatopathy
  - Non-specific response to variety of extra-hepatic disease processes
  - Inflammatory infiltrate in **portal areas and in parenchyma**
  - No hepatocellular necrosis
  - Neutrophils acutely
  - Lymphoplasmacytic chronically

66

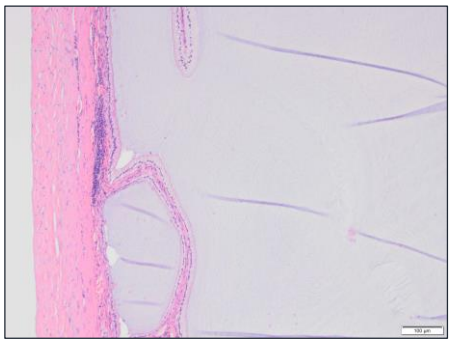
## Cholangitis- take-home points

- Increasingly recognized in dogs
- Increased ALP & ALT most common
- Consider bacterial component
- In some cases may be the result of long-term gallbladder disease

67

## Cholecystitis

- Choleystitis
  - Acute or chronic
  - Non-suppurative or suppurative
  - Gas or choleliths→ infection



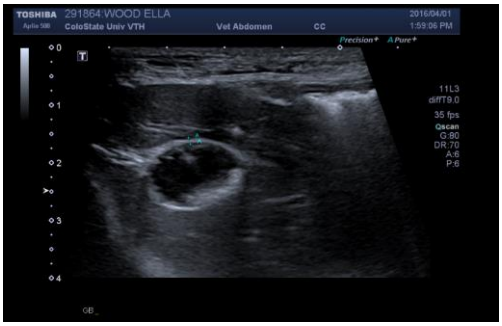
Necrotizing cholecystitis

- Acute or chronic
- Infection, TE, blunt trauma, GBM, EHBDO(choleliths, neoplasia)
- Gas or choleliths→ infection

68

## Imaging

- Ultrasound findings
  - Thickened GB wall (>3 mm)
  - Immobile GB sediment
  - +/- choleliths, EHBDO, emphysema, hepatic abnormalities




69

## Bacterial cholecystitis

**Characterization, treatment, and outcome of bacterial cholecystitis and bactibilia in dogs**

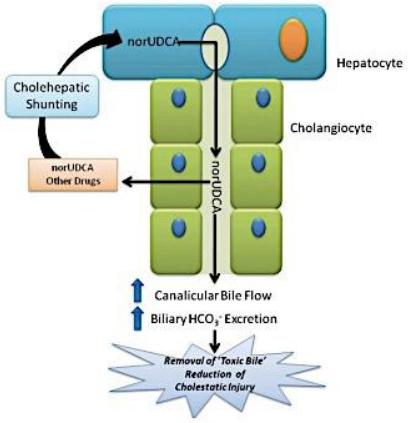
*YA Lawrence, CG Ruaux, S Nemanic, M Milovancev*
*J Am Vet Med Assoc 2015;246:982-989*

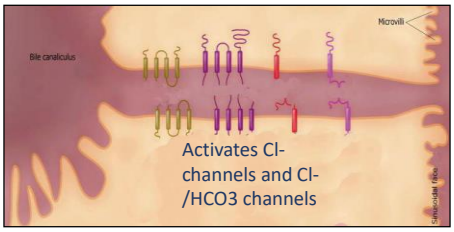
- *10 case dogs; 30 controls dogs (hepatobiliary disease)*
- *5/10 dogs were dachshund*
- *Case dogs: > degree of biliary sediment and more likely to have immobile biliary sludge*
- *Cytologic exam of bile routine dx in dogs with hepatobiliary disease and sludge*

70

# Therapy

- Cholecystectomy
  - Treatment of choice
- Medical management
  - Antibiotics
  - Hepatosupportive medications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# Clinical characteristics and histology of cholecystectomised dogs with nongravity-dependent biliary sludge: 16 cases (2014-2019)

*Journal of Small Animal Practice* (2021) **62**, 478–488
DOI: 10.1111/jsap.13302

A. D. Viljoen[1,*], A. Tamborini[†], P. J. Watson[‡] and N. H. Bexfield[‡]

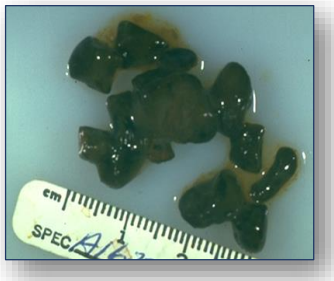
- Retrospective case series
- All dogs had NDBS, clinical signs were inappetence and exercise intolerance
- 11/16 dogs had normal biochemistry panel
- 12 dogs had cholecystitis, 13 had enteritis (duodenum)
- After cholecystectomy, clinical improvement in 81% of dogs

72

# Cholelithiasis

- May be incidentally discovered
- Hypercholesterolemia and hypertriglyceridemia independent risk factors

Calcium carbonate, bilirubin, less commonly cholesterol

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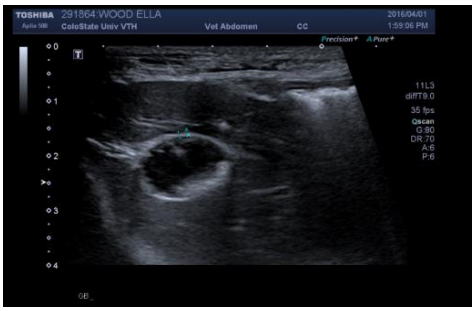
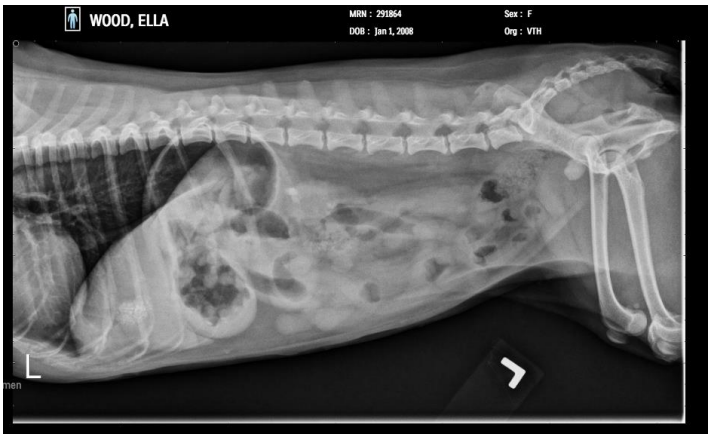
# Imaging

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# Choleliths and infection

- B-glucuronidase

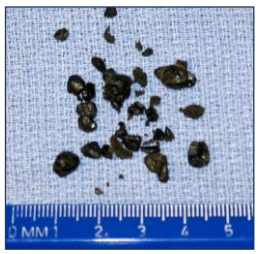

Conjugated bilirubin (soluble)

Free bilirubin
Glucoronic acid

Ca2+

Calcium bilirubinate (insoluble)

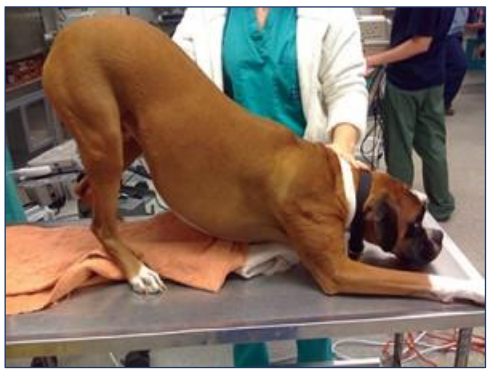
+/- other bile pigments / metals



75

# Treatment

- Medical vs surgical
- Concern for chronic pain
- Remove nidus
- Cholecystoenterostomy ↑↑↑ complications



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RETROSPECTIVE STUDIES

## Cholelithiasis in the Dog: Prevalence, Clinical Presentation, and Outcome

Patricia M. Ward, MVB, MRCVS, Kieran Brown, BVM&S, MRCVS, Gawain Hammond, MA, VetMB, MVM, CertVDI, DECVDI, FHEA, MRCVS, Tim Parkin, BSc, BVSc, PhD, DECVPH, FHEA, FRCVS, Sarah Bouyssou, MRCVS, Mark Coia, BVMS, MRCVS, Genziana Nurra, MRCVS, Alison E. Ridyard, BVSc, DSAM, DECVIM-CA, MRCVS

J Am Anim Hosp Assoc
2020; 56:152–158

- Retrospective cross-sectional study over 8 years identified 68 dogs with cholelithiasis
- Medical records were available for 61 dogs
- Cholelithiasis was incidentally discovered in 23/61 (86.9%) of dogs
- Follow up was available for 39 dogs, 3 of which developed complications attributed to cholelithiasis within 2 year period

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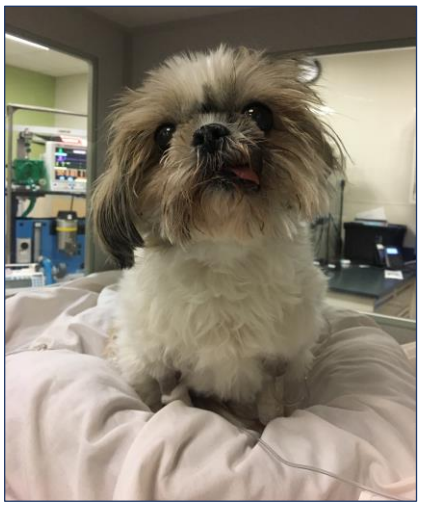
## Ella



January 2016

8 year old FS Shih Tzu

Not eating, vomiting x 4 days

PE: icterus

78

# Ella

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| Tech 1 Comments: | Icteric. | | |
| Nucleated Cells | | 25.0 | H |
| Bands | 2% | 0.5 | H |
| Neutrophils | 77% | 19.3 | H |
| Lymphocytes | 8% | 2.0 | |
| Monocytes | 11% | 2.8 | H |
| Eosinophils | | 0.0 | L |
| nRBC | 2% | 0.5 | H |
| Neutrophils auto | | 19.3 | |
| Plasma Protein | | 7.6 | H |
| HCT | | 37 | L |
| RBC | | 5.83 | |
| Cell Hgb | | 12.3 | L |
| MCV | | 64 | |
| RDW | | 14.5 | |
| HGB | | 12.7 | L |
| MCHC | | 34 | |
| CHCM | | 33 | |
| Reticulocyte auto | 1% | 36.2 | |
| CH-r | | 21.5 | L |
| MCV-r | | 87 | |
| Polychromasia | | | |
| Target cells | | Few | |
| PLT | | 272 | |
| MPV | | 11.7 | |
| Clumped Pits | | Few | |

| | |
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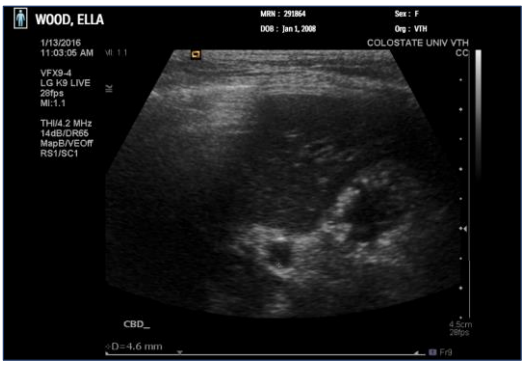
| Tech 1: | LTS |
| Tech 1 Comments: | Hemolyzed, Icteric |
| GLUCOSE | 114 |
| BUN | 13 |
| CREATININE | 0.8 |
| PHOSPHORUS | 3.6 |
| CALCIUM | 9.5 |
| MAGNESIUM | 2.0 |
| TOTAL PROTEIN | 5.6 |
| ALBUMIN | 3.0 |
| GLOBULIN | 2.6 |
| A/G RATIO | 1.2 |
| CHOLESTEROL | 370 H |
| T-BILIRUBIN | 9.5 H |
| ALP | 5398 H |
| ALT | 185 H |
| AST | 94 H |
| CK | 204 |
| GGT | 61 H |
| SODIUM | 145 |
| POTASSIUM | 4.01 |
| CHLORIDE | 103.5 L |
| BICARBONATE (HCO3-) | 20.7 |
| ANION GAP | 25 H |
| CALCULATED OSMOLALITY | 288 |
| IRON | 88 |
| HEMOLYSIS | 97 |
| ICTERUS | 11 H |
| LIPEMIA | 14 |

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# Ella

| | |
|---|---|
| Interpretation(s) | FINAL<br>*BILE*<br>*BACTERIA, FILAMENTOUS* |
| Pathologist(s): | ALM |

| | |
|---|---|
| Interpretation(s) | *or neoplastic etiologies are observed.*<br>FINAL<br>*CHOLESTASIS*<br>*SUPPURATIVE INFLAMMATION* |
| Pathologist(s): | ALM |

**LIVER**

| Animal | Sample | Test / Analyte | Result | Comment | Report Date |
|---|---|---|---|---|---|
| 291864 1 | **Bile** | 552 - VTH - Anaerobic & aerobic Culture and Sensitivity / Aerobic & Anaerobic Culture and Sensitivity | E. coli | Moderate growth Susceptibility complete | 01-14-16 |
| 291864 1 | Swab | 552 - VTH - Anaerobic & aerobic Culture and Sensitivity / Aerobic & Anaerobic Culture and Sensitivity | No Anaerobes Isolated | Final 01/19/2016 | 01-14-16 |

**Treatment in hospital :**
**Enrofloxacin, Metronidazole IV**
**Maropitant**
**Buprenorphine**

**Treatment TGH:**
**Enrofloxacin**
**Denamarin**
**Ursodiol**

80

# Ella

**Chemistry**

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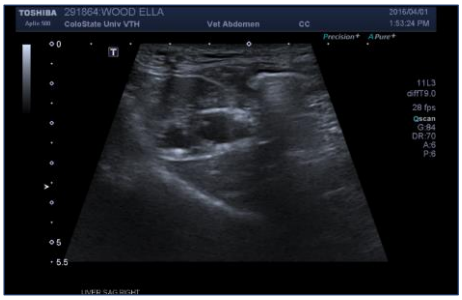
| Tech 1: | LTS | TLW | DL | CLP | LTS | |
| Tech 1 Comments: | Hemolyzed, lipemic. | | Grossly Hemolyzed Icteric. | Moderately hemolyzed. | Hemolyzed, Icteric | |
| GLUCOSE | 103 | 80 | 91 | 75 | 114 | 70 - 115 mG/dL |
| BUN | 16 | 17 | 12 | 13 | 13 | 7 - 30 mG/dL |
| CREATININE | 0.8 | 0.8 | 0.6 | 0.5 L | 0.8 | 0.6 - 1.6 mG/dL |
| PHOSPHORUS | 3.9 | 5.6 | 4.2 | 5.4 | 3.6 | 2.5 - 6.0 mG/dL |
| CALCIUM | 10.1 | 10.7 | 9.8 | 9.4 | 9.5 | 9.0 - 11.5 mG/dL |
| MAGNESIUM | 2.1 | 2.3 | 2.0 | 2.3 | 2.0 | 1.8 - 2.4 mG/dL |
| TOTAL PROTEIN | 6.3 | 6.5 | 6.0 | 5.6 | 5.6 | 5.0 - 7.0 G/dl |
| ALBUMIN | 3.9 | 3.5 | 3.1 | 2.7 L | 3.0 | 3.0 - 4.3 G/dl |
| GLOBULIN | 2.4 | 3.0 | 2.9 | 2.9 | 2.6 | 1.5 - 3.2 G/dl |
| A/G RATIO | 1.6 | 1.2 | 1.1 | 0.9 | 1.2 | 0.9 - 2.4 RATIO |
| CHOLESTEROL | 218 | 332 H | 347 H | 381 H | 370 H | 130 - 300 mG/dL |
| T-BILIRUBIN | 0.2 | 1.2 H | 1.4 H | 2.4 H | 9.5 H | 0.0 - 0.2 mG/dL |
| ALP | 375 H | 4342 H | 4957 H | 5524 H | 5398 H | 15 - 140 IU/L |
| ALT | 37 | 226 H | 257 H | 202 H | 185 H | 10 - 90 IU/L |
| AST | 24 | 72 H | 53 H | 50 H | 94 H | 15 - 45 IU/L |
| CK | 156 | 945 H | 220 | 284 H | 204 | 50 - 275 IU/L |
| GGT | 7 | 73 H | 67 H | 72 H | 61 H | 0 - 9 IU/L |
| SODIUM | 145 | 145 | 144 | 143 | 145 | 142 - 152 mEQ/L |
| POTASSIUM | 4.73 | 5.52 H | 5.74 H | 4.91 | 4.01 | 3.9 - 5.4 mEQ/L |
| CHLORIDE | 109.0 | 103.3 L | 106.2 L | 104.0 L | 103.5 L | 108 - 118 mEQ/L |
| BICARBONATE (HCO3-) | 18.4 | 18.3 | 20.0 | 20.2 | 20.7 | 15 - 25 mEQ/L |
| ANION GAP | 22 | 29 H | 24 H | 24 H | 25 H | 12 - 23 mmol/L |
| CALCULATED OSMOLALITY | 290 | 290 | 288 | 284 | 288 | mOsm/Kg |
| IRON | 155 | 76 L | 94 | 100 | 88 | 80 - 270 uG/dL |
| HEMOLYSIS | 174 H | 29 | 213 H | 182 H | 97 | 0 - 100 mG/dL |
| ICTERUS | 0 | 2 H | 2 H | 3 H | 11 H | 0 - 1 mG/dL |
| LIPEMIA | 78 | 22 | 5 | 16 | 14 | 0 - 80 mG/dL |

April 2016

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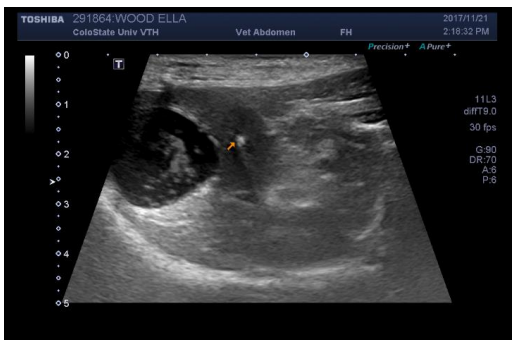
| Tech 1: | CLP | TLW | MJM | MJM | CLP | |
| Tech 1 Comments: | Hemolyzed, lipemic. | Grossly Hemolyzed | Moderately hemolyzed. Grossly lipemic | | | |
| GLUCOSE | 110 | | 128 H | 117 H | 117 H | 70 - 115 mG/dL |
| BUN | 11 | | 8 | 5 L | 8 | 7 - 30 mG/dL |
| CREATININE | 0.9 | | 0.7 | 0.5 L | 0.9 | 0.6 - 1.6 mG/dL |
| PHOSPHORUS | 4.2 | | 3.6 | 3.9 | 5.2 | 2.5 - 6.0 mG/dL |
| CALCIUM | 10.7 | | 8.9 L | 8.9 L | 10.7 | 9.0 - 11.5 mG/dL |
| MAGNESIUM | 2.1 | | 1.6 L | 1.7 L | 2.1 | 1.8 - 2.4 mG/dL |
| TOTAL PROTEIN | 6.8 | | 5.0 | 4.7 L | 6.3 | 5.0 - 7.0 G/dl |
| ALBUMIN | 3.7 | 3.7 | 2.8 L | 2.9 L | 3.8 | 3.0 - 4.3 G/dl |
| GLOBULIN | 3.1 | | 2.2 | 1.8 | 2.5 | 1.5 - 3.2 G/dl |
| A/G RATIO | 1.2 | | 1.3 | 1.6 | 1.5 | 0.9 - 2.4 RATIO |
| CHOLESTEROL | 255 | | 215 | 213 | 333 H | 130 - 300 mG/dL |
| T-BILIRUBIN | 0.1 | | 0.1 | 0.1 | 0.2 | 0.0 - 0.2 mG/dL |
| ALP | 670 H | 568 H | 687 H | 801 H | 1373 H | 15 - 140 IU/L |
| ALT | 23 | 44 | 374 H | 471 H | 994 H | 10 - 90 IU/L |
| AST | 25 | | 33 | 43 | 40 | 15 - 45 IU/L |
| CK | 195 | | 349 H | 552 H | 143 | 50 - 275 IU/L |
| GGT | 0 | | 11 H | 21 H | 36 H | 0 - 9 IU/L |
| SODIUM | 144 | | 145 | 145 | 146 | 142 - 152 mEQ/L |
| POTASSIUM | 4.74 | | 4.97 | 4.70 | 5.05 | 3.9 - 5.4 mEQ/L |
| CHLORIDE | 105.9 L | | 109.4 | 111.0 | 107.1 L | 108 - 118 mEQ/L |
| BICARBONATE (HCO3-) | 19.4 | | 18.7 | 21.8 | 20.2 | 15 - 25 mEQ/L |
| ANION GAP | 23 | | 22 | 17 | 24 H | 12 - 23 mmol/L |
| CALCULATED OSMOLALITY | 287 | | 289 | 287 | 290 | mOsm/Kg |
| IRON | 155 | | 44 L | 31 L | 114 | 80 - 270 uG/dL |
| HEMOLYSIS | 321 H | 321 H | 128 H | 13 | 19 | 0 - 100 mG/dL |
| ICTERUS | 0 | 0 | 0 | 0 | 0 | 0 - 1 mG/dL |
| LIPEMIA | 564 H | 23 | 327 H | 2 | 16 | 0 - 80 mG/dL |

October 2016- diarrhea, weight loss
July 2017- more weight loss
September 2017- diarrhea
November 2017- vomiting, lethargic

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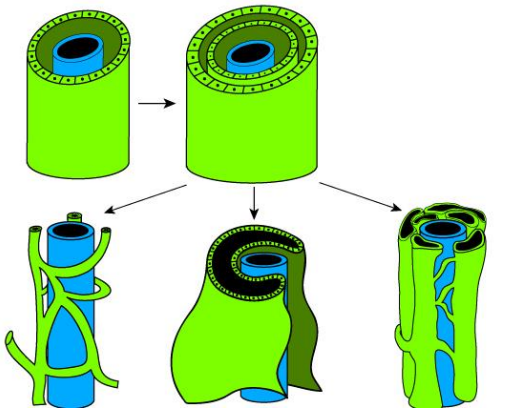
# Ductal plate

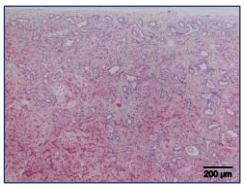
- Double layer of epithelium
- Embryonic precursor to interlobular and intralobular bile ducts
- Abnormalities of development ➔ wide variety of disorders

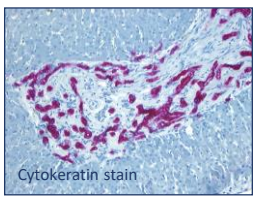



83

# Ductal plate malformations

- Congenital hepatic fibrosis➔ maturation arrest of small interlobular bile ducts

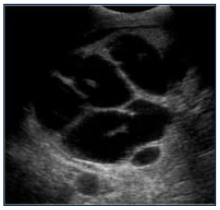


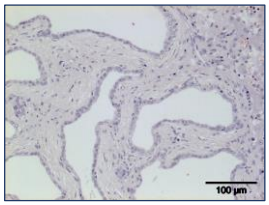




- **Numerous small and irregular bile ducts**
- **Diffuse peri-portal to bridging fibrosis**
- Reduction in portal venules

Caroli's disease ➔ maturation arrest of medium intralobular bile ducts

- **Wildly dilated bile ducts**,
- +/-fibrosis (variable degree)
- +/- renal cysts

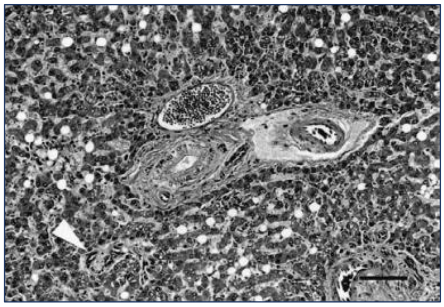





84

# Portal venous hypoplasia (PVH) with portal hypertension (PH)

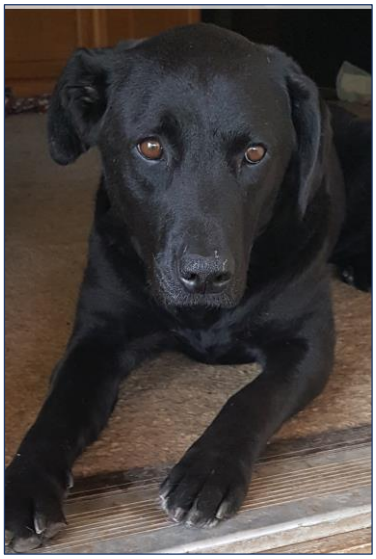
- Ductal plate malformation? Not technically
- Development of biliary system mirrors that of the portal vasculature
- Lesions in both systems are common to all the diseases
- Used to be referred to as non-cirrhotic portal hypertension



- **Multiple arterioles**
- **Portal veins smaller than normal or absent in most portal tracts (rarely enlarged)**
- Fibrosis variable (usually not bridging),
- Hepatocellular atrophy
- Bile ducts usually normal (occasional small bile duct proliferation)

85

# Scarlett



4 year old FS Labrador mix

March 2018: Abnormal behavior (staring) & gait, PU/PD x 6 months

PE: unremarkable

CBC:
PLT 143 x 10^3/ul

Biochemical profile:
ALT 614 IU/L
ALP 441 IU/L

86

# Scarlett

| Chemistry | | |
|---|---|---|
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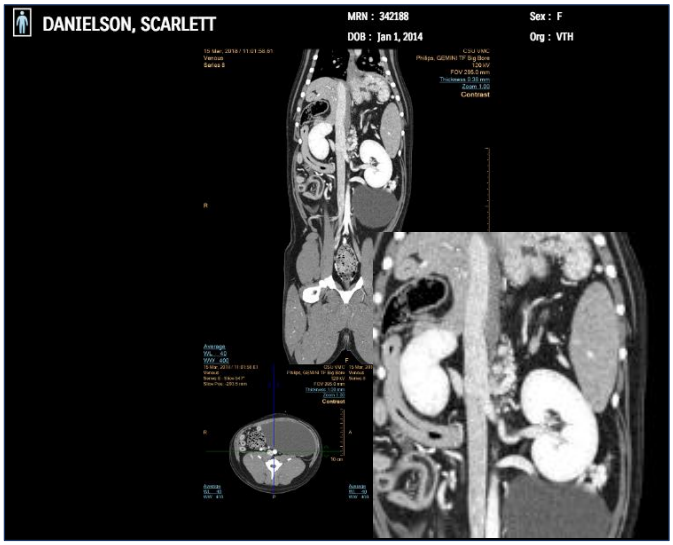
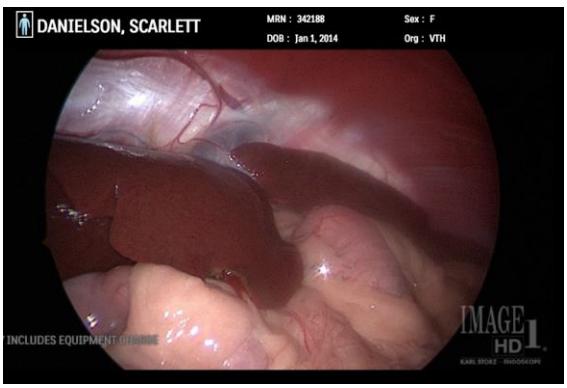
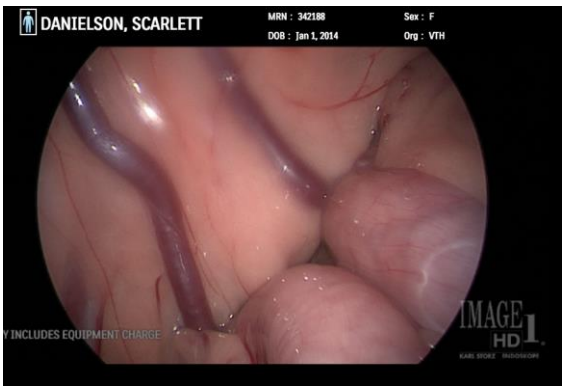
| Invoice: | 4006883 | |
| Barcode: | 1801319759 | |
| Collected: | 1/31/2018 15:10 | |
| Accessioned: | 1/31/2018 15:21 | |
| Completed: | 1/31/2018 15:51 | |
| Tech 1: | JMJ | |
| Tech 1 Comments: | "Fasted/Pre: 3:10pm." | |
| CK | | |
| HEMOLYSIS | 31 | |
| ICTERUS | 1 | |
| LIPEMIA | 3 | |
| BILE ACIDS | 244 | H |




87

# Scarlett




FINAL DIAGNOSIS:
Liver: Marked chronic diffuse hepatopathy with **bridging and dissecting portal fibrosis** as well as lobular atrophy, biliary hyperplasia, and rare individualized hepatocyte necrosis.

88

## Scarlett

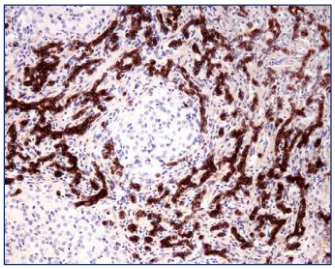
- Therapy:
- Liver diet
- Lactulose
- Amoxicillin
- Denamarin

- 3-year survival so far

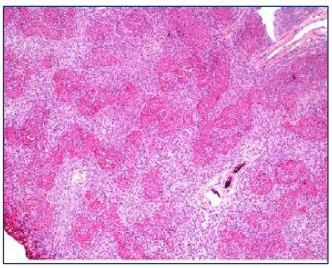
**Congenital hepatic fibrosis in 5 dogs**

*DL Brown, T Van Winkle, T Cerere, S Rushton, C Brachelente, JM Cullen*
*Vet Path 2010;47:102-107*

- *All dogs severe bridging fibrosis w marked increase in number of small bile ducts*
- *Cytokeratin 7 IHC*
- *4/5 abnormal portal vein profiles*

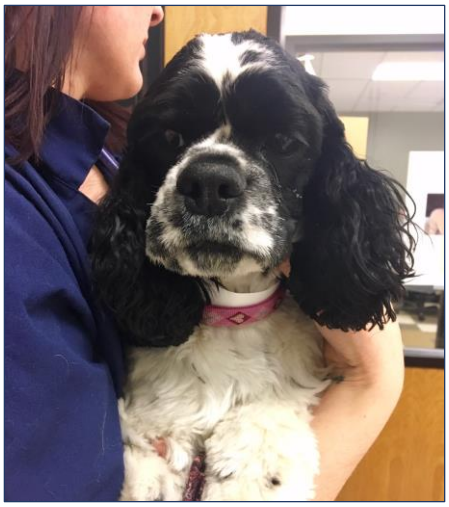


Cytokeratin 7



89

## Lily



11 month old FS cocker spaniel

Intermittent vomiting, pre-spay labwork abnormal, liver bx at the time of spay ; hx of ascites

PE: BCS 3/9

90

# Lily

**Chemistry**

| | | | |
|---|---|---|---|
| Status: | FINAL | | |
| Invoice: | 3935624 | | |
| Barcode: | 1704056704 | | |
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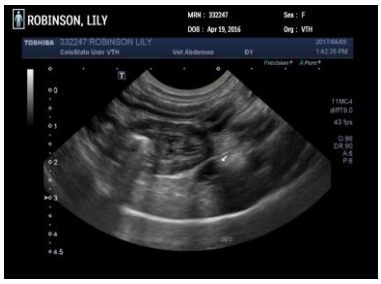
| Accessioned: | 4/5/2017 13:05 | | |
| Completed: | 4/5/2017 14:29 | | |
| Tech 1: | CLP | | |
| GLUCOSE | 87 | | 70 - 115 mG/dL |
| BUN | 6 | L | 7 - 30 mG/dL |
| CREATININE | 0.4 | L | 0.6 - 1.6 mG/dL |
| PHOSPHORUS | 5.0 | | 2.5 - 6.0 mG/dL |
| CALCIUM | 9.6 | | 9.0 - 11.5 mG/dL |
| MAGNESIUM | 1.8 | | 1.8 - 2.4 mG/dL |
| TOTAL PROTEIN | 5.5 | | 5.0 - 7.0 G/dl |
| ALBUMIN | 3.2 | | 3.0 - 4.3 G/dl |
| GLOBULIN | 2.3 | | 1.5 - 3.2 G/dl |
| A/G RATIO | 1.4 | | 0.9 - 2.4 RATIO |
| CHOLESTEROL | 125 | L | 130 - 300 mG/dL |
| T-BILIRUBIN | 0.3 | H | 0.0 - 0.2 mG/dL |
| ALP | 148 | H | 15 - 140 IU/L |
| ALT | 272 | H | 10 - 90 IU/L |
| AST | 50 | H | 15 - 45 IU/L |
| CK | 142 | | 50 - 275 IU/L |
| GGT | 8 | | 0 - 9 IU/L |
| SODIUM | 152 | | 142 - 152 mEQ/L |
| POTASSIUM | 4.35 | | 3.9 - 5.4 mEQ/L |
| CHLORIDE | 114.3 | | 108 - 118 mEQ/L |
| BICARBONATE (HCO3-) | 20.9 | | 15 - 25 mEQ/L |
| ANION GAP | 21 | | 12 - 23 mmol/L |
| CALCULATED OSMOLALITY | 298 | | mOsm/Kg |
| IRON | 149 | | 80 - 270 uG/dL |
| HEMOLYSIS | 7 | | 0 - 100 mG/dL |
| ICTERUS | 1 | | 0 - 1 mG/dL |
| LIPEMIA | 3 | | 0 - 80 mG/dL |

Bile acids

Pre-prandial: 277 umol/L
Post-prandial: 383 umol/L


91

Microscopic Description: Examined are several sections of liver, and a sample of fat. In the liver sample, hepatic lobules appear decreased in size, with increased proximity of portal triads, and there is mild attenuation of hepatocellular cords with relative dilation of sinusoids. **Portal veins are often inapparent, and there is associated proliferation of arterioles and small ductules.** Scattered pigment-laden macrophages are present. Hepatocytes sometimes contain small vacuoles and finely granular pigment. All tissue was submitted for processing.

**Microscopic Findings: Liver: Venous hypoplasia with arteriolar hyperplasia and lobular atrophy.**

Comment: The hepatic lesions are consistent with portal hypoperfusion, with inapparent portal vein profiles and reduplication of arterioles. The changes support the presence of a vascular anomaly. In the absence of an identifiable shunt, portal vein hypoplasia (also referred to as microvascular dysplasia) is a primary consideration.

**COPPER: 2010 ppm**

92

## Non-cirrhotic portal hypertension/PVH with PH

**Idiopathic noncirrhotic portal hypertension in dogs: 33 dogs (1982-1998)**

*SE Bunch, SE Johnson, JM Cullen*
*J Am Vet Med Assoc 2001;218:392-399*

- *Histologic lesions indistinguishable from congenital portosystemic shunt or portal vein hypoplasia*
- *Follow up 19 dogs*
  - *4 euthanized, 3 dogs with duodenal ulcer; 1 died unknown causes*
  - *13 dogs clinically normal 5 months to 9 years*
  - *Ascites resolved in 12/13 dogs*

93

## Delilah

- 10 month old FI Golden Retriever
- Anomalous vessel noted during CT thorax for evaluation of Cor triatriatum dexter
- Microhepatica also noted
- CT angiography, spay & liver biopsy

94

# Delilah

FINAL DIAGNOSIS: Liver: **Cirrhosis.**

COMMENTS: This liver meets the criteria for cirrhosis with the conglomeration of nodular regeneration, marked biliary hyperplasia, fibrosis, and inflammation. This represents end-stage liver damage from many possible underlying causes, and may be related to the clinically-reported right heart disease in this case.

95

# Delilah

"We received the stained slides this week and were quite lucky that our pathology team was having a "liver day". John Cullen (one of the leading veterinary liver pathologists) was there visiting for a resident training event. Together Patricia Pesavento (UCD), John Cullen (NCSU) and Jim Maclaghlan (UCD) carefully reviewed the slides for your dog. They concluded that the changes are **diagnostic for congenital hepatic fibrosis (ductal plate malformation) and they all agreed that the changes identified could NOT be secondary to right heart changes.** I hope that this information is helpful in deciding how to move forward! It was a really beneficial session with the three of them and they had total agreement on these findings."

96

CONGENITAL HEPATIC FIBROSIS VS. CIRRHOSIS

Congenital hepatic fibrosis
No evidence of nodular regeneration
Numerous bile duct profiles in ductal plate configuration

97

## When to suspect ductal plate malformations

- Young to middle aged dog
- Portal hypertension
  - Ascites- typically a modified transudate (result of portal hypertension)
  - +/- hepatic encephalopathy
- Markedly elevated bile acids are typical
  - No evidence of a congenital PSS
  - Multiple acquired shunts common
    - Need a skilled ultrasonographer or CT angiogram – acquired shunts can be easily missed

98

## Treatment of ductal plate malformations

- We don't have good ways of addressing the underlying disease
- Treat the complications

99

## Treatment

Hepatic Encephaolopathy
- ❖ Diet
- ❖ Lactulose
- ❖ Antibiotics

Portal Hypertensive Gastropathy
- ❖ Best treatment unknown in dogs
- ❖ May consider acid suppression (proton pump inhibitor)

RAAS Activation and Ascites
- ❖ Sodium Restriction
- ❖ Spironolactone is diuretic of choice

Treatment of underlying disease

- ❖ Anti-fibrotics
  - ❖ Silymarin
  - ❖ ARB?

100

## More information on ductal plate malformations and other biliary tract disease

REVIEW

# Canine hepatobiliary anatomy, physiology and congenital disorders

J. A. Jaffey[1]

Department of Specialty Medicine, College of Veterinary Medicine, Midwestern University, Glendale, Arizona, USA

[1]Corresponding author email: jjaffe@midwestern.edu

*Journal of Small Animal Practice* (2021), 1–9
DOI: 10.1111/jsap.13410

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## Questions?

sjw@msu.edu

References in proceedings or upon request

102

# CURRENT CONCEPTS IN CANINE BILIARY TRACT DISEASE

SARA WENNOGLE, DVM, PhD, DACVIM-SAIM
*Michigan State University, East Lansing MI*

## The Biliary Tract in Health

The biliary tract is divided into intra- and extra-hepatic components. The intrahepatic biliary tract contains the hepatic canaliculi, bile ductules, intralobular ducts and interlobar ducts. The extra-hepatic biliary tract contains the hepatic ducts, cystic duct, gallbladder (GB), common bile duct, and the pancreaticobiliary sphincter (commonly referred to as the sphincter of Oddi). In the dog, bile is formed in hepatocytes and actively secreted into the bile caniliculi from which it flows to the interlobular ducts and eventually to the lobar ducts. The lobar ducts give rise to the hepatic ducts. There is substantial variation in the number of hepatic ducts and their various anastomoses. From the hepatic ducts bile flows to the cystic duct and into the gallbladder. The cystic duct is an important landmark because it distinguishes the hepatic ducts from the common bile duct. Several of the hepatic ducts terminate in the common bile duct (CBD), which transports bile to the duodenum through the sphincter of Oddi. The normal canine CBD is approximately 3mm in diameter. Its length is approximately 5 cm in the medium-sized dog, including a duodenal intramural length of 1.5 to 2 cm before termination at the major duodenal papilla, the location of the sphincter of Oddi. The major duodenal papilla includes the opening of the CBD, and in approximately 75% of dogs the orifice of the accessory pancreatic duct. [1-3]

The gallbladder is blind-ended vesicle that stores bile. It has a volume of approximately 1 milliliter per kilogram of body weight. The rounded apical end is termed the fundus, the middle portion the body, and the tapered region where the GB connects to the cystic duct is referred to as the neck. The GB lies in a fossa between the right medial and quadrate lobes of the liver. It has a thin wall composed of mucosa, lamina propria, smooth muscle, and serosa. Columnar epithelial cells line the mucosa. These cells reabsorb water and electrolytes allowing for concentration and increased viscosity of the bile. Submucosal glands secrete mucus that lubricates the bile. Importantly, the GB has end-artery vascularity via the cystic artery, and a lack of collateral arterial blood supply, making it particularly susceptible to ischemic injury. GB filling occurs continuously through hepatic secretion of bile and passive distension of the GB.[1]

Bile is composed of water, bile salts (conjugated bile acids), fats (including cholesterol, fatty acids), phospholipids and other miscellaneous substances. Unconjugated bile acids are cytotoxic and can induce significant tissue damage. Bile salts allow digestion of dietary fats by emulsifying them into micelles therefore bile is also an important part of the absorption of fat-soluble substances, such as vitamins A, D, E and K. Bile also serves as the route of excretion for cholesterol, bilirubin, and copper. Bile has a role in the neutralization of stomach acid as it enters the duodenum, and has bacteriostatic activity. Bile is released via GB contraction, which is primarily initiated by cholecystokinin in response to fats and proteins entering the small intestine. Cholecystokinin also induces relaxation of the sphincter of Oddi, which regulates flow of bile into the duodenum. Vagal parasympathetic innervation also plays an important role in contraction of the GB. Somatostatin, secreted at the pancreas, pylorus, and duodenum in response to fats in the small intestine facilitates GB filling and inhibits its contraction. [1-4]

## General Approach to Canine Biliary Disorders

While diseases of the biliary tract are generally less common than parenchymal hepatic conditions in the dog, recent veterinary literature would suggest that the prevalence and/or recognition of canine biliary tract disease is increasing. Biliary tract disorders in the dog are generally grouped into 4 major categories: cholestasis, diseases of the GB, cholangitis, and congenital diseases of the biliary tract (including cystic disease, atresia, and malformation of the bile ducts).[5] Cholestasis is a significant feature of many hepatobiliary disorders in the dog including gallbladder mucocele (GBM), cholangitis, extrahepatic bile duct obstruction (EHBDO), and chronic hepatitis. Consequences of cholestasis include the disruption of the normal conjugation of bile acids, resulting in cytotoxic effects to hepatic and non-hepatic cells, hepatic retention of compounds normally excreted in bile, changes in the gut microbiome, altered intestinal permeability, and fat malabsorption.[6] The other categories of biliary tract disease in the dog will be discussed specifically below.

Clinical signs of biliary tract disease in the dog can be non-specific including decrease or loss of appetite, vomiting, diarrhea, weight loss, polyuria, polydipsia and/or lethargy. Clinical signs may wax and wane, or in certain cases the dog can present in critical condition with evidence of shock. Additional signs may include jaundice, apparent abdominal discomfort and bleeding tendencies. Physical examination may reveal poor body condition, jaundice, hepatomegaly, palpation of an abdominal mass effect, abdominal pain, detection of a fluid wave, and/or elevated body temperature. Detection of acholic feces in a dog with jaundice is concerning for bile duct obstruction.

Plain radiography may be occasionally be useful in the diagnosis of biliary tract disease, including in the case of radiopaque stones or the identification of air in the biliary tract. In addition, mineralization of the biliary tract may be seen in cases of biliary carcinoma (‘porcelain gallbladder’). Ultrasonography has proved to be an invaluable tool in the evaluation of the biliary tract in dogs and cats.[2, 4] However, ultrasound has limitations. Abdominal ultrasonography was recently demonstrated to have a low sensitivity for the detection of rupture of the GB in dogs with GBM.[7] In a separate study contrast-enhanced ultrasonography was demonstrated to be more sensitive for the detection of GB wall necrosis and rupture when compared to routine ultrasonography. [8] Additionally, gallbladder ultrasound is only modestly sensitive and not specific for detecting bacterial infection of bile in dogs.[9] MRI and CT imaging are becoming more common in the diagnosis of hepatobiliary and pancreatic disorders in small animals.[10] A prospective pilot study evaluated CT for the detection of pancreatitis in 10 dogs and found that CT identified more features characterizing pancreatic abnormalities when compared to US. Additionally thrombi were detected in 3 dogs with CT and 0 dogs with ultrasonography.[11] However, further studies are needed to determine the usefulness of MRI and CT in diagnosing pancreatic and biliary disease in dogs.

Percutaneous ultrasound-guided cholecystocentesis can be an important component of the diagnostic work-up of biliary tract disease. Sampling of bile for cytologic evaluation and bacterial culture may negate the need for more invasive procedures in some cases. A recent study described 51 cats and 201 dogs that had percutaneous ultrasound-guided cholecystocentesis

performed (some cases had the procedure performed more than once for a total of 300 procedures).[12] The complication rate was low. Major complications occurred in 8/300 procedures (7/8 cases died or were euthanized) including bile peritonitis in 2/300 procedures. Another study described 56 and 78 client-owned cats and dogs that underwent percutaneous ultrasound-guided cholecystocentesis with clinically relevant complications only occurring in 2 dogs. Both dogs developed bile peritonitis.[13] Thus, percutaneous ultrasound-guided cholecystocentesis is generally safe, but should be performed with extreme caution in patients with suspect necrosis of the GB wall and owners should be warned of the very rare complication of cardiopulmonary arrest.

Because of the liver's unique and complex role in hemostasis, a variety of coagulation abnormalities are possible in the context of canine biliary tract disease. Bleeding or clotting tendencies can be observed. Traditionally bleeding is expected as a complication of EHBDO (due to vitamin K deficiency) but a study assessing thromboelastography in dogs with EHBDO identified all dogs as hypercoagulable.[14] The state of coagulation in dogs with EHBDO may depend on how long obstruction has been present.

Treatment of biliary tract disease relies on correct identification and treatment of the underlying disorder. If EHBDO or rupture of the biliary tract is present, emergency surgery is recommended. Concurrent liver abnormalities are common with GB disease therefore hepatic biopsies should be obtained at the time of surgery. If biliary tract infection is definitively identified or suspected, antimicrobial choice should be based on culture and sensitivity, or on the targeting of known pathogens of the biliary tract, respectively. Recent studies have identified the most common pathogens of the canine biliary tract to be *Escherichia coli, Enterococcus* spp., *Clostridium* spp., and *Streptococcus* spp. *Corynebacterium* spp., *Proteus* spp. *Bacillus licheiformis, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* have also been identified as pathogens in canine bile, among others. [13,15,16] Non-specific therapies appropriate for biliary tract disease are outlined in Table 1. [17] Recently, a study showed that in-vitro administration of N-acetylcysteine (NAC) significantly decreased the viscosity of canine bile.[18] However, the efficacy of this treatment for clinical cases of biliary sludge or gallbladder mucocele is unknown.

Angiotensin –receptor blockers, such as losartan or telmisartan, have been demonstrated to attenuate hepatic fibrosis in rodent models. However, involvement of the RAS system in the pathogenesis of hepatic fibrosis has not yet been demonstrated in the dog, so it is not clear whether these medications would be beneficial. Pirfenidone is an anti-fibrotic drug that has been shown to decrease fibrosis in humans with chronic hepatitis C. Whether this drug would be safe and effective for dogs with fibrosing liver disease is unknown at this time.[19] Fibrates have been demonstrated to improve cholestatic liver disease in humans.[20]

In human patients, biliary system pain can be significant and difficult to distinguish from other causes of pain. Additionally, disorders of the gallbladder have a wide range of clinical presentations, and can be challenging to diagnose. Accordingly, disorders of the biliary tract should be considered in canine patients with non-specific signs for which an obvious cause is not readily apparent.

**Table 1. Selected medications indicated in the treatment of cholestatic hepatopathies**

| Agent | Mechanisms of Action | Dosing | Side Effects |
|---|---|---|---|
| S-adenosylmethione | Anti-apoptotic<br>Antioxidant: increases glutathione<br>Modulates cytokine expression | 20 mg/kg/d, PO (best administered in fasted state) | None |
| Ursodeoxycholic acid | Choleretic<br>Anti-apoptotic<br>Immunomodulatory<br>Replacement of hepatotoxic bile acids | 10-15 mg/kg/d, PO (best given with food)<br><br>*Can increase dose to 20-30 mg/kg/d (divided q 12 h) with severe cholestasis | Vomiting (rare)<br><br>*may increase bioavailability of cyclosporine |
| Silymarin | Antifibrotic<br>Choleretic<br>Anti-inflammatory<br>ROS scavenger | Silymarin: 20-50 mg/kg/d (divided q 6-8 h, PO)<br><br>Siliphos: 3-6 mg/kg/d, PO | None |
| Vitamin E | Anti-oxidant<br>Anti-inflammatory | 10-15 IU/kg/d, PO (alpha-tocopherol acetate) | None at recommended doses |

## Specific Disorders

### *Gallbladder Mucocele*

Over the last 20 years GBM has emerged as the most common and poorly understood biliary disease of the dog. GBM affects older dogs of either sex and occurs most commonly in pure breed dogs. Shetland sheepdogs, Border terriers, Cocker spaniels, miniature schnauzers, Pomeranians, Chihuahuas, and others are predisposed. [21-24] Risk factors include the presence of endocrinopathies (hypothyroidism and hyperadrenocorticism)[25], hyperlipidemia[26], and GB dysmotility[27]. Exogenous glucocorticoid usage may also contribute to mucocele formation.[4] One study also suggested that imidacloprid use in Shetland sheepdogs was a risk factor.[28] Mucocele formation is characterized by excess secretion of gel-forming mucins and accumulation of rubbery mucus in the GB. Clinical signs are highly variable. The classic ultrasonographic appearance of immobile bile with a finely striated or stellate pattern within the GB lumen makes the diagnosis generally straightforward in many cases. However, in cases where GBM is accompanied by other GB pathology, the ultrasonographic appearance may vary. Recent studies have suggested contrast-enhanced ultrasonography can aid in the detection of gallbladder wall edema, necrosis or rupture (but do not necessarily improve detection of GBM). [8, 29] CT cholangiography in dogs with GBM was recently demonstrated to be effective for evaluating the right and left hepatic ducts, common hepatic duct, cystic duct, gallbladder and common bile duct.[30] This imaging modality may prove useful in the screening of patients for EHBDO prior to laparoscopic cholecystectomy.

Importantly, echogenic biliary material is relatively common in dogs. In one study 77 healthy dogs were screened for biliary sludge and 45 were identified. Over the course of 12 months, all dogs remained asymptomatic and there was no significant change in gravity dependency of the sludge over one year.[31]

In cases of GBM the incidence of concurrent cholecystitis has been reported as 17-40%. [22,23,33] In a recent study of 25 dogs with GBM 68% of cases were found to have concurrent cholecystitis, which was moderate-severe in 53% of cases.[34] Concurrent bacterial infection has been reported in 3-67% of cases with GBM. [9,14,21-23,32,33] It is generally considered to be a consequence of GBM rather than a cause. A study using fluorescent *in-situ* hybridization (FISH) on GB tissue in cases of GBM reported 32% of cases were FISH positive despite only one dog having a positive bacterial culture.[34] Importantly, bacterial LPS can damage the GB epithelium in dogs.[35] EHBDO can occur in cases of GBM. Thus, duodenotomy and flushing of the CBD should be considered at the time of surgery for GBM. GB rupture is another possible complication of GBM. In these cases ultrasound may reveal a discontinuous GB wall, peri-cholecystic fluid, free abdominal fluid, and/or hyperechoic fat.[22, 33] Dogs with GB rupture frequently have neutrophilia with a left shift, high blood lactate, and one study showed that dogs with rupture have higher serum ALT, ALP and bilirubin.[22] Importantly, however, a recent study reported that (40%) of dogs with confirmed ruptured biliary tracts had a serum bilirubin concentrations within the normal reference range.[36] Recently, GBM has been associated with proteinuria, thus it is recommended to screen patients with GBM for proteinuria.[37]

Extrahepatic bile duct obstruction and GB rupture are clear indications for surgery. Additionally, cholecystectomy should be performed in all clinically symptomatic dogs as they are at risk of life threatening complications. In particular, since septic bile peritonitis carries a worse prognosis than non-septic bile peritonitis the suspicion of biliary infection in a patient with GBM should result in swift initiation of antibiotics and surgery to remove the GB.[38] Elective cholecystectomy should be strongly considered in dogs with GBM that are asymptomatic but have abnormal serum biochemistry. GBM are unlikely to resolve with medical therapy alone and the presence of the mucocele likely indicates a functional GB abnormality. Furthermore, cholecystectomy performed at a time when the dog is feeling well is likely to have a more successful outcome versus at a time when the dog is compromised. A median mortality rate of 27% has been reported in dogs undergoing cholecystectomy for the treatment of GBM.[14, 21-23, 33] Recently, Youn et al. reported mortality rates for 70 dogs that underwent biliary tract surgery at a companion animal hospital over 6 years.[39] Many of the dogs had GBM. In this study dogs receiving elective biliary tract surgery had a mortality rate of 2%, compared to 20% in dogs undergoing non-elective biliary tract surgery. Cholecystectomy was considered not elective when dogs were icteric or had evidence of EHBDO. Thus, delay in pursuing cholecystectomy in dogs may be the reason for the high mortality rates that have been reported. Bile peritonitis has been inconsistently associated with mortality in cases of GBM. However, in a recent study of 219 dogs of GBM, dogs with gallbladder rupture with bile peritonitis at the time of surgery were 2.7 times more likely to die than dogs without gallbladder rupture and bile peritonitis.[7] Concurrent hepatic abnormalities are common in dogs with GBM [32], therefore liver biopsy should always be performed at the time of cholecystectomy. Bacterial culture of bile/inspissated material should be performed, culture of hepatic and gallbladder tissue can also be considered. If

documented, infection should be treated with appropriate antibiotics for at least 4 weeks. Some dogs may benefit from long-term therapy with hepatosupportive medications.

Laparoscopic cholecystectomy (LC) is becoming increasingly available and a recent study reported successful LC in 71/76 dogs with benign GB disease. Mortality was low (2 dogs intraoperatively and 2 dogs postoperatively) despite inclusion of dogs with jaundice and gallbladder rupture.[40]

Medical therapy may be attempted in dogs with GBM who are asymptomatic dogs and have normal liver enzyme activities and function parameters, however resolution of GBM following medical treatment has only been reported in a handful of dogs. One dog's GBM resolved after being tapered off immunosuppressive doses of corticosteroids and treatment with ursodeoxycholic acid and antibiotics. One Shetland sheepdog's GBM resolved following treatment with low fat diet, ursodeoxycholic acid and SAMe,[21] and two additional dogs treated with ursodeoxycholic acid, SAMe, antibiotics, and thyroid supplementation had resolution of their GBM.[35] If medical treatment is to be pursued risk factors (e.g. endocrinopathies, hyperlipidemia) need to be identified and treated. A low fat diet should be initiated as well as choleretic and hepatoprotectant therapies. A 4-week course of broad-spectrum antibiotics appropriate for the biliary tract is often considered. Therapeutic failure should be considered if the ultrasound appearance of the GBM does not change or worsens after 6 months of therapy, or if the dog develops clinical signs or increases in serum liver enzyme activities or serum bilirubin.

Overall, surgical therapy is the preferred treatment. Of dogs surviving at least 14 days after diagnosis of GBM, median survival times were 1802 days, 1340 days, and 203 days, for the surgical, medical, and medical then surgical treatment groups, respectively, and differed significantly.[41]

Gookin and colleagues recently demonstrated that mucocele formation is the result of excess secretion of a gel-forming mucin (Muc5ac) by the GB epithelium.[42] The properties of this mucus are similar to mucus observed in humans with cystic fibrosis, and interestingly, piglets and ferrets with knockout of the cystic fibrosis transmembrane regulatory protein (CFTR) develop GB disease that is very similar to GBM in dogs.[6] This protein is primarily responsible for hydration of mucus, which suggests that promoting hydration of mucus may help combat mucocele formation. In another study investigating the pathogenesis of GBM formation, Gookin and colleagues conducted a mass spectrometric characterization of the serum and hepatic bile duct metabolome in dogs with and without mucocele formation. They found significant changes in the metabolome of dogs with mucocele formation compared to those without mucocele.[43] Of particular importance was the finding that a number of compounds that stimulated biliary fluid secretion were significantly decreased in dogs with mucocele formation, and they suggested that supplementation of these compounds should be examined for possible medical therapy of GBM.

### *Cholecystitis/Cholangitis*

Canine cholecystitis/cholangitis appears to be more common than previously suspected. Still, it is significantly less common than hepatic parenchymal disease in the dog. In a recent multicenter

retrospective study conducted over 7 years, 27 dogs were identified as having bacterial cholangitis, cholecystitis, or both. Over the same time period at the same institutions, 460 cases of hepatitis were documented.[16]

Cholecystitis can be acute or chronic, non-suppurative or suppurative, and is associated with a wide range of clinical signs and laboratory abnormalities. Predisposing factors in humans include bile stasis, biliary neoplasia, bacterial or parasitic disease, and gallbladder mucocele. While studies have failed to find factors that predict positive bile or liver cultures, the presence of gas (emphysematous cholecystitis) or choleliths more reliably indicate infection. A recent case report described ganglioneuromatosis, a rare exuberant hyperplastic proliferation of ganglion cells and nerves, in the gallbladder of a dog with cholecystitis.[44] Another recent case report describes 'limy bile' syndrome in a dog with bacterial cholecystitis. This is an uncommon disorder in human medicine characterized by radiopaque material in the gallbladder, and less commonly, the bile ducts. This material is composed of calcium carbonate and the pathogenesis is unclear. In the case of this 11-year-old dog with 'limy bile' syndrome, cholecystectomy was curative.[45] Necrotizing cholecystitis is considered a more severe manifestation of the disease with an increased risk of complications and a higher mortality rate.[1] It can present with or without GB rupture or can also be a more chronic syndrome where adhesions between the GB and adjacent viscera are seen. Bacterial infection, thromboembolism, blunt abdominal trauma, GBM, and extrahepatic biliary duct obstruction secondary to cholelithiasis, neoplasia or other causes should be considered. Ultrasound findings in cases of cholecysitis include thickened GB wall and immobile GB sediment.[1] Less commonly, choleliths, evidence of EHBDO, and/or emphysema of the GB may be detected. In one study 10 dogs with bacterial cholecystitis or cholangitis on histologic analysis or bactibilia on cytologic exam were compared to 30 dogs without bactibilia. Dachshunds were overrepresented among breeds affected. Case dogs had a greater degree of biliary sediment formation and were more likely to have immobile biliary sludge when compared to control dogs.[15] Medical management with antibiotics and hepatosupportive medications can be attempted but cholecystectomy is considered the treatment of choice in most cases.

The World Small Animal Veterinary Association (WSAVA) has classified canine and feline cholangitis into 4 groups: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis, and chronic cholangitis associated with liver fluke infestation. Involvement of the hepatic parenchyma is variable so the term cholangitis is preferred to the term cholangiohepatitis. Neutrophilic cholangitis is most common, and is suspected to result from ascending bacterial infection from the intestine. Acutely it is characterized by peri-portal neutrophilic inflammation and edema. In the chronic phase of disease a mixed inflammatory infiltrate in the portal areas may be observed in addition to bile duct proliferation and fibrosis. Lymphocytic cholangitis is a common disorder in the cat, but apparently rare in the dog. Destructive cholangitis is associated with loss of biliary ducts and resulting inflammation and portal fibrosis. It may result from an idiosyncratic reaction to drugs (in particular sulfonamides), however certain viral infections and other toxic insults have been associated with destruction of the biliary epithelium. Destructive cholangitis typically results in severe cholestasis and subsequent icterus and may produce acholic feces, which is typically a feature reserved to extra-hepatic biliary obstruction.[5]

Infection with liver flukes can cause acute and chronic cholangitis. Dogs are less frequently affected than cats. Dogs from Texas, North Carolina, Louisiana, Florida, Kansas and Indiana

have been diagnosed with infection with *Heterobilharzia americana*, a schistosomal fluke.[46] Dogs are infected via skin penetration of cercariae released from snails which migrate through the dog as schistosomula to the lungs (within 5-9 days) and to the liver (7-45 days). They mature in the liver and adults migrate to the mesenteric veins and the bowel. Clinical signs are non-specific and liver enzyme activity is variable. Azotemia, hyperglobulinemia, and ionized hypercalcemia can be seen. Frequent hematologic abnormalities include thrombocytopenia and lymphopenia with eosinophilia being uncommon. Histopathologic characteristics include dilated larger bile ducts and marked periductal and portal fibrosis. Slight to moderate inflammation may be seen within the ducts as well as in portal areas. Treatment is with praziquantel at 20-25 mg/kg, po, q 8 h, for 3 days. Prednisolone at anti-inflammatory doses is often used to reduce fluke-associated inflammation. Secondary bacterial infections can occur as a consequence of migrating or dying flukes, therefore broad-spectrum antibiotic coverage is often recommended during anthelmintic therapy. Finally, ursodeoxycholic acid can be used to promote hydrocholeresis, and vitamin E and SAMe may be considered for hepatic support. Prognosis is generally favorable.[4]

A recent study described a population of dogs with cholangitis or cholangiohepatitis. In a 10-year period, 54 dogs with histopathological evidence of cholangitis or cholangiohepatitis were identified.[47] Almost all dogs (53/54) had neutrophilic cholangitis, with a single case of lymphocytic cholangitis. The hepatic parenchyma was involved in 9/54 (16.7%) of cases. Most cases were chronic and had some degree of fibrosis (mostly portal) and 42.6% of dogs had evidence of intrahepatic biliary obstruction with periductular fibrosis. Bile duct hyperplasia was common (79.6% of cases). Thirty-one dogs had concurrent GB and/or gastrointestinal biopsies performed. Concurrent gallbladder disease was detected in 25 dogs including 11 dogs with cholecystitis, 7 dogs with GB infarction, 2 dogs with GBM, and 1 dog with GB neoplasia. Biliary cultures were performed in 36 cases, 17 of which were positive; liver cultures were performed in 25 cases, 11 of which were positive. Many of the dogs were receiving antimicrobial therapy at the time of sample collection. The majority of dogs were medium-sized and middle aged. The results of laboratory testing in these dogs was as expected and reaffirmed that the presence of hyperbilirubinemia in combination with an inflammatory leukogram, fever, or abdominal effusion should increase clinical suspicion for biliary tract disease. Ultrasonographic findings included hepatomegaly, mixed echogenicity or hyperechoic liver, GB distension, increased GB sediment, dilated bile ducts, and changes indicative of pancreatitis (13 dogs), enteritis (6 dogs), and gastritis (5 dogs). The high incidence of concurrent GB disease led the authors to speculate that cholangitis may be the result of GB disease. In addition, dogs that underwent cholecystectomy had a decreased risk of death, highlighting the importance of the GB in cases of canine cholangitis. Dogs in this study received various medical therapies including antibiotics, liver support medications/nutriceuticals however the effects of these medications could not be evaluated due to the retrospective nature of this study. Whether canine cholangitis is a primary disease or a sequela of other biliary disease remains unclear.

### *Cholelithiasis*

Cholelithiasis describes a pathological condition of stone formation within the gallbladder, intrahepatic or extrahepatic bile ducts. Choleliths are often discovered incidentally in asymptomatic dogs.[48] A recent retrospective study performed over 8 years reported on 61 dogs

with cholelithiasis. In 53/61 (86.9%) dogs choleliths were discovered incidentally, and in 39 cases long-term follow-up was available. Only 3/39 dogs developed complications related to their choleliths within a 2-year period.[49] However, cases of cholelithiasis can be life threatening such as when EHBDO occurs, or when cholelithiasis is associated with sepsis. Recently serum concentrations of leptin, cholesterol, and triglycerides were found to be higher in dogs with cholelithiasis compared to healthy controls. Hypercholesterolemia and hypertriglyceridemia were independent risk factors for the development of choleliths. Leptin and leptin receptor expression were also upregulated in the gallbladder tissues of cholelithiasis patients.[50] Choleliths in dogs typically contain calcium carbonate, bilirubin, and less commonly, cholesterol. These are typically known as 'pigment stones' and are often not radiographically apparent as they do not contain enough mineral to be visible. Black pigment stones are primarily composed of bilirubin polymers secondary to prolonged hyperbilirubinemia. Brown-pigment stones predominantly contain calcium bilirubinate and are typically associated with biliary stasis and bacterial infection, in which inspissated material acts as a nidus for formation. Excess mucin helps entangle bilirubin and calcium bilirubinate polymers into choleliths.[4] An increased incidence in miniature poodles and miniature schnauzers has been suggested.[50] Choleliths may or may not be radiographically apparent. Cholecystoliths > 2mm can be detected via ultrasonography. Ultrasonographic detection of choledocoliths is more challenging.[4]

Medical treatment of cholelithiasis involves treatment with broad-spectrum antibiotics and choleretic therapies (ursodeoxycholic acid and SAMe). When choleliths are associated with cholecystitis, occluding the common bile duct, or causing cystic duct obstruction, surgical intervention is typically required. Cholecystectomy is typically recommended as retaining a diseased GB may increase the risk of recurrence of choleliths. Prognosis may worsen when a cholecystoenterostomy is required due to inability to resolve an obstruction in the common bile duct, as those dogs need to be monitored long-term for the development of septic cholangitis.

In humans with cholelithiasis, pain may be intense but intermittent. In some dogs diagnosed with cholelithiasis careful consideration of their clinical history may reveal signs of intermittent vague pain for years. Therefore, cholelithiasis should be a differential for dogs with vague intermittent clinical signs.

### *Biliary Tract Neoplasia*

Hepatobiliary neoplasia represents only 0.6 to 1.3% of all cancers in the dog.[51] Further, while bile duct tumors are the most common type of hepatic neoplasm in the cat, primary tumors of the biliary tract are less common than hepatic parenchymal neoplasms in the dog. Biliary cystadenomas can be single or multifocal and malignant transformation has been reported in humans. Large cystadenomas can be completely or partially surgically removed and carry a good prognosis.

Biliary adenocarcinomas are the second most common hepatic neoplasms in the dog. Females and Labrador retrievers appear to be predisposed. Claudin-7 has been shown to be an excellent immunohistochemical marker to distinguish biliary adenocarcinoma from hepatocellular carcinoma in the dog.[1] Biliary adenocarcinomas are slowly progressive and not typically diagnosed until biliary obstruction has occurred at which time metastatic disease is typically

present. If disease is confined to one lobe, surgical resection can be considered. If disease is diffuse, the prognosis is generally poor.[51] Recently microwave ablation for the treatment of non-surgically resectable hepatic neoplasia was described in 5 dogs, one of which had diffuse biliary carcinoma and survived for at least 21 months following treatment.[52]

***Bile Duct Obstruction***

Primary intrahepatic bile duct obstruction is rare in the canine but may be seen in severe cases of cholangitis, such as destructive cholangitis. Intrahepatic bile duct obstruction more commonly occurs as a consequence of extra-hepatic bile duct obstruction, which is significantly more common in the dog. Extra-hepatic bile duct obstruction may occur as a consequence of number of conditions including pancreatitis (most common cause), duodenitis, duodenal foreign body, neoplasia of the pancreas, duodenum or biliary tract, cholecystitis/choledochitis, cholelithiasis, gallbladder mucocele, parasitic infection, fibrosis or bile duct stricture. If obstruction persists >6 weeks it results in peribiliary fibrosis, remodeling of the liver, and the eventual development of portal hypertension. If EHBDO is complete it may result in the development of white bile within the bile duct or gallbladder due to the absence of bilirubin pigment in bile. The biliary tree may also become colonized by bacteria.[4]

Clinical signs are variable but may include lethargy, fever, vomiting, and change in appetite (inappetant vs polyphagic due to fat malabsorption). Jaundice will typically develop within 4 hours of complete EHBDO. Bleeding tendencies may be apparent and ulceration at the pyloric-duodenal junction is common in chronic cases (develop sooner in the cat vs. dog). Hemogram may reveal non-regenerative or regenerative anemia, neutrophilic leukocytosis with or without a left shift. Serum ALP and GGT activities usually increase within 8-12 hours of obstruction and as bile stagnates within the biliary tract serum ALT and AST activities increase as well. Hypercholesterolemia is common reflecting impaired cholesterol elimination and possible increased cholesterol biosynthesis. If present, bleeding tendencies are typically responsive to vitamin K administration. One study suggested that lung injury secondary to systemic inflammatory response syndrome is common in dogs with EHBDO and may contribute to perioperative mortality.[53]

EHBDO is typically diagnosed based on compatible clinical signs, hematologic and biochemical abnormalities and ultrasonography. CT and MRI have been increasingly used to evaluate for pancreatitis in the dog. These modalities can also evaluate the CBD for distension and obstruction, as well as detect portal venous thrombosis.[54] Percutaneous ultrasound-guided cholecystography may also prove useful in the future. Surgical decompression of the biliary system is often necessary for treatment of EHBDO. Furthermore, surgical intervention may be necessary to treat the underlying disease causing EHBDO or to remove a nidus of infection or inflammation. Dogs undergoing biliary surgery for treatment of EHBDO have had a reported mortality rate of around 30%. However, if surgical biliary diversion is required reported mortality rates range from 25-73%. Early recognition and intervention are said to improve outcomes.[4] In dogs with pancreatitis causing EHBDO, surgical intervention is controversial.[55] Obstruction will resolve in most dogs with pancreatitis and EHBDO over the course of a few weeks, however if obstruction is persistent it can lead to biliary cirrhosis. Therefore, stenting of the CBD at the sphincter of Oddi is sometimes considered and has been successful in some

cases. However, risk of mortality may be as high as 50%.[4] Dogs with biliary tract infection are at risk for hypotension and endotoxic shock during anesthesia and surgery. Success with endoscopic retrograde cholangiography and endoscopic retrograde biliary stenting has been reported in 4 of 7 research dogs and 1 of 2 patients with EHBDO. Although the operators were experienced the procedures were described as technically challenging.[56] Transhepatic ultrasound-guided aspiration of the GB for decompression can be performed in patients in which surgery is declined or cannot be performed. However, performing this procedure in a patient with EHBDO comes with a high risk of focal or generalized peritonitis.[4]

***Ductal Plate Malformations***

The ductal plate is a double layer of epithelium that serves as the embryonic precursor to the interlobular and intralobular bile ducts. In humans, abnormalities in the development of bile ducts lead to a wide variety of disorders. Many of these disorders have an autosomal dominant pattern of inheritance. In addition to the changes in their bile ducts affected individuals have varying amounts of hepatic fibrosis and may have concurrent renal and skeletal abnormalities. The pathogenesis of the development of fibrosis in this context is incompletely understood.[57]

Ductal plate malformations that have been described in the dog include congenital hepatic fibrosis and Caroli's disease.[58,59] In humans congenital hepatic fibrosis develops as a consequence of maturation arrest of small interlobular bile ducts. Maturation arrest of the medium intralobular bile ducts results in Caroli's disease. The genetics, pathogenesis, and exact classifications of these ductal plate abnormalities in dogs are unknown at this time.

Congenital hepatic fibrosis is characterized histologically by diffuse peri-portal to bridging fibrosis, numerous small and irregular bile ducts, and a reduction in the number of portal venules. The lesions of the bile ducts bear resemblance to the developing ductal plate. Inflammation and cholestasis are generally absent. In humans, portal hypertension with acquired portosystemic shunts and ascites are common as a consequence of hepatic fibrosis and/or insufficiency of the portal vasculature. Hepatic enzyme activity and function testing are variable. Bile acids are generally elevated in patients with ductal plate abnormalities, in particular in dogs with acquired shunting. The first complete report of congenital hepatic fibrosis in dogs was in 2010.[58] Five dogs were identified. All dogs had evidence of portal hypertension, four cases had multiple extrahepatic portosystemic shunts. Histologic exam revealed bridging fibrosis with numerous small irregular bile duct profiles in all 5 dogs. Ductules are tortuous with irregular to absent lumina, with ball like protrusion of the wall into the lumen in some cases. Mild arteriolar hyperplasia was present in 4 dogs, and portal vein profiles were hypoplastic to absent in 4 cases. Cytokeratin 7 immunohistochemistry identified the structures as immature ducts rather than arterioles or progenitor cells. Significant expression of proliferating cell nuclear antigen (PCNA) was not observed as would be expected with biliary hyperplasia seen as a ductal reaction to hepatic injury. Clinical case outcomes were not described in this series of 5 dogs. Pillai et al described ductal plate malformations in 30 Boxer dogs, suggesting an increased prevalence in the breed.[60] Of the 30 dogs, only two had the Caroli's phenotype of saccular dilations involving the intralobular bile ducts as well and 11 dogs fit the criteria for congenital hepatic fibrosis. Several of the dogs in this study had concurrent congenital abnormalities such as intrahepatic vascular

malformations, left-sided liver lobe atrophy, and absence of a gallbladder. In addition, 35% of cases had increased hepatic copper concentrations.[60]

During embryogenesis, the development of the biliary system mirrors that of the portal vasculature, likely explaining why ductal plate malformations are often accompanied by abnormalities in the portal vasculature. Although not technically a ductal plate malformation, non-cirrhotic portal hypertension (NCPH) is often discussed in the same context as congenital hepatic fibrosis and Caroli's disease. This disease process is now typically referred to as portal vein hypoplasia (PVH) with portal hypertension (PH). Unlike portal vein hypoplasia, PVH with portal hypertension is often reported in large-breed dogs. As the name suggests dogs present with portal hypertension often accompanied by ascites. The development of acquired portosystemic shunting is common. In the early 2000's 33 cases of NCPH were reported.[61] Dogs were presented for ascites, gastrointestinal signs and polydipsia. Imaging revealed microhepatica, peritoneal effusion, and multiple anomalous vessels. Histology revealed abnormal lobular portal tracts with multiple arterioles and smaller than normal or absent portal veins in most cases. The amount of fibrosis was variable, bile ducts were usually normal and inflammation was absent to minimal. Long-term survival was reported for many dogs in the study. Dogs were treated with therapies to lessen ascites, control clinical signs of hepatic encephalopathy (when present) and prevent gastric and duodenal ulceration secondary to intrahepatic portal hypertension.[61]

Importantly, the presenting clinical signs of ductal plate abnormalities and PVH with PH (previously referred to as NCPH) can be similar to that of end-stage liver disease. Histopathologically, congenital hepatic fibrosis is often confused with cirrhosis. Unlike dogs with cirrhosis dogs with congenital hepatic fibrosis do not have evidence of nodular regeneration and the bands of fibrotic tissue have numerous bile ducts in a ductal plate configuration.[56] Many dogs with ductal plate abnormalities and NCPH can have a favorable prognosis if managed appropriately so it is critical that every attempt be made to distinguish these abnormalities from end-stage liver disease. Additionally, it is important to remember that dogs with congenital portosystemic shunts will not present with portal hypertension and ascites. Finally, it is likely that these diseases are under-recognized in clinical veterinary medicine and increased reporting of disease may help improve recognition.

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