### Case Summary

- **Signalment:**
  - “Beau” 6 yr N/M standard poodle

- **History:**
  - Mild intermittent right front leg lameness
  - No current medications

- **Plan:**
  - Sprain/strain Rx NSAID
  - Pre-treatment blood work

### Case Summary

- **Elevated liver enzymes identified**
  - ALT 479
  - AST 69
  - ALP 535

- **Modified plan:**
  - Postpone NSAID therapy
  - Begin liver support therapy
  - Recheck enzymes in approximately 1 month
Hepatic Necrosis Associated with Carprofen in 21 Dogs: JAVMA 1999

- 13/21 Labrador retrievers
- Mean onset of signs: 2-3 wks
- 5/21 dogs died, others recovered
- Rare idiosyncratic drug reaction
- NSAID Rx recommendations:
  - Pretreatment liver enzymes
  - Re-check ALT in 10-14 days
  - Stop NSAID if sick
- Abnormal liver enzymes do not increase risk of hepatic toxicity

Case Summary

- 1 month recheck
  - Liver enzymes
    - ALT 732
    - AST 84
    - ALP 640
  - Bile acids
    - Pre 48 (N< 10)
    - Post 87 (N<20)
- Abdominal ultrasound

Case Summary

- Clotting times: normal
  - PT, APTT, Platelets
  - Buccal mucosal bleeding time
- Laparoscopic biopsy
- Histology
  - Chronic hepatitis
- Hepatic copper
  - 655 ppm (N<450)
- Hepatic culture
  - Aerobes and anaerobes negative
Review of 150 Consecutive Liver Biopsies at CSU

Chronic Hepatitis - Cirrhosis
n = 35

Chronic Hepatitis

- Characterized by:
  - Moderate to severe chronic mixed inflammation
  - Hepatocellular necrosis
  - Fibrosis is a poor prognostic indicator

Beau 6 yr N/M standard poodle

Hepatic CU 655 µg/g liver

Chronic Hepatitis

- Known etiologies:
  - Copper
  - Infectious
    - (Leptospirosis, others?)
    - (ICH adenovirus, others?)
  - Drugs (primidone, phenobarbital, NSAIDs?)
  - Genetic
- Unknown etiology:
  - Idiopathic (immune-mediated?)
**Immune Mediated Mechanism of CH**

- Hepatocyte Insult
- Injury
- Antigen Release
- Antibodies
- Cytotoxic Lymphocytes
- Immuneocyte
- Macrophage Processing

**Chronic Hepatitis**

**Breed Predisposition:**
- Doberman pinscher
- Bedlington terrier
- West Highland White terrier
- Cocker spaniel (American & English)
- Standard poodle
- Labrador retriever
- Dalmatian
- Scottish terrier
- English Springer spaniels

*Andersson JSAP 32: 1991*

**Copper Associated Hepatitis**

- Doberman pinscher
- Bedlington terrier
- West Highland White terrier
- Cocker spaniel (American & English)
- Standard poodle
- Labrador retriever
- Dalmatian
- Scottish terrier
- English Springer spaniels

*Andersson JSAP 32: 1991*
Hepatic Copper Determination

- Histochemical stains
- Copper quantitation
  - Normal < 450 µg/g
  - Metabolic > 1000 µg/g
- 5 mm diameter liver sample
- Paraffin embedded histo samples

Chronic Hepatitis in Standard Poodles

- Females > males
- Abnormal ALT ~ 3 to 4 years
- Copper not involved
- Etiology unknown
- Studies underway at CSU
  - Genetic testing
  - Morphologic description

Chronic Hepatitis - Clinical Features

- Age
  - 4 to 11 years
  - Mean 7.5 years
- Sex
  - Females > males (60/40)
Laboratory vs Clinical Signs

<table>
<thead>
<tr>
<th>Severity</th>
<th>Normal</th>
<th>Chronic Hepatitis</th>
<th>Cirrhosis</th>
<th>End Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Enzymes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of no clinical signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Findings in CH

<table>
<thead>
<tr>
<th>Variation From Normal</th>
<th>Normal</th>
<th>Chronic Hepatitis</th>
<th>Cirrhosis</th>
<th>End Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose BUN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting times</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prognosis for CH

- Early diagnosis improves prognosis
- Guarded with secondary complications or cirrhosis:
  - HE
  - Ascites
  - GI ulceration
  - Hypoalbuminemia
  - Clotting abnormalities

Sevelius: JSAP 36:1995
Raffan: JVIM 23:2009

Solve It! Series
The Case of the Limping Poodle

October 2011

The Four Goals of Therapy

- Treat 1st Etiology
- Diet
- Chronic Hepatitis
- Specific Therapy
- Hepatic Support

Hepatic Disease

- Palatability
- Meet caloric needs
- Protein restriction
  - Adequate protein is essential, restriction only with protein intolerance
- Liver diets
  - Low in copper
  - Moderate protein
  - Antioxidants

Basic Guidelines

- Feed multiple small meals a day
- Find a palatable diet
  - High quality, highly digestible protein (i.e. veterinary GI, liver / geriatric diets)
  - Avoid high fiber diets
- Feed low copper diet (with Cu toxicity)
  - >5 mg/kg (ppm) DM (liver diets)
Therapy is directed at controlling:

- Inflammation
- Copper
- Fibrosis
- Cholestasis
- Infection

Corticosteroids and CH

- Positive benefits
  - Anti-inflammatory
  - Choleretic
  - Inhibits fibrosis
  - Improves appetite
- Negative aspects
  - Steroid hepatopathy
  - Sodium & water retention
  - Precipitate early death

Corticosteroid Therapy in Chronic Hepatitis

- 151 Dogs
- 56 Dead < 1 week
- 95 Alive > 1 week
- 58 Steroids + other treatment
- 37 No steroids + other treatment

Strombeck: JAVMA 193: 1988
Chronic Hepatitis Survival

Steroid Rx ~ 3X longer survival
Could the ~ 25% having a
prolonged survival represent
immune mediated disease?

Glucocorticoid Therapy

- **Prednisone**
  - 1 to 2 mg / kg / day
  - Taper to 1-0.5 mg / kg EOD
- **Questions:**
  - Length of treatment?
  - Effectiveness of therapy?
- **Alternate therapy**
  - Azathioprine
  - Cyclosporine

Immunosuppressive Therapy

- Steroid intolerant or Rx failure:
  - Azathioprine
    - 2 mg/kg/day then taper to EOD
  - Idiosyncratic hepatopathy
    - Cyclosporine
      - 5 mg/kg bid ález q 24h
  - Gingival hyperplasia
Immunosuppressive Therapy

- 13 dogs treated
  - 12/13 had 71% reduction in ALT
  - 6/10 treated > 60 days had normal ALT
  - 5/6 with clinical signs improved
  - 8/8 with ascites or hyperbilirubinemia resolved
  - 5/13 had adverse effects: GI (3), papillomatosis (1) and gingival hyperplasia (1)

Copper Associated Hepatitis

- Hepatic copper > 1000 µg/g  
  (N<400 µg/g)
  - Copper chelator
  - Low copper diet
  - After chelation treat with zinc and/or diet
- Secondary copper accumulation < 1000 µg/g
  - Zinc therapy
  - Low copper diet

Hepatic Copper Chelators

- Penicillamine
  - 10 - 15 mg / kg BID
- Trientine
  - Penicillamine 10 - 15 mg / kg BID
Bile Acids Cause Liver Damage

- Bile acids increase in disease
  - Most are hydrophobic bile acids
  - Act as membrane detergents
- Hydrophilic “good” bile acid
  - Ursodeoxycholic acid
  - Ursodiol
  - Displaces toxic bile acids
  - Protective properties

Ursodeoxycholic Acid

- Hepatoprotective
- Anti-inflammatory
- Antioxidant
- Choleretic
  - Upregulates canalicular membrane transporters
- Immune modulation

Ursodeoxycholic Acid

- Chronic Hepatitis
- Feline cholangitis
- Other cholestatic liver disease?
- Mucocele?
- Not choleliths
**Ursodeoxycholic Acid**
- Adjunct liver therapy
- Dosage: 10-15 mg/kg q 24 h
- Low toxicity
- No concern with potential bile duct obstruction

**Antibiotics and Liver Disease**
- Kupffer cell dysfunction could result in secondary bacterial seeding
- Culture liver biopsies
- Antibiotic therapy may be rational in advanced hepatic disease
- Kupffer cells prevent portal derived infections

**Empirical Antibiotic Selection**
- Amoxicillin
- Cephalosporins
- Metronidazole
  - Immunosuppressive activity?
  - Both renal & hepatic metabolism
- Dosage: 7.5-10 mg/kg bid
Hepatic Fibrosis

- Fibrosis inhibits normal hepatic function
- Antifibrotic activity
  - Glucocorticoids
  - Penicillamine
  - Colchicine?
  - Losartan
    - Angiotensin II inhibitor
    - 0.25-0.5 mg/kg/da

Liver Support

- Provides hepatic protection and an environment conducive for optimal hepatic and antioxidant function
- ~ 45% of dogs and cats with liver disease have glutathione depletion
  - Center et al: JVIM 2000
- Proven beneficial agents:
  - Vitamin E
  - Milk thistle
  - SAMe
**Vitamin E (d\(\alpha\)-tocopherol)**
- Essential nutrient
  - Mammals can’t synthesize
  - Membrane associated antioxidant
- Decreased vitamin E concentrations in some dogs with liver disease
- Protects against oxidative damage from Cu and Fe
- 10 IU/Kg q 24 hrs

**S-Adenosylmethionine (SAMe)**
- Produced in the body
- Highest levels in the liver
- Uses:
  - Liver support
  - Acute hepatic toxicity
  - Hepatotoxic drug therapy

**Herbal Remedy - Milk Thistle**
- Antioxidant
  - Prevents membrane lipid peroxidation
  - Increases hepatic GSH concentration
- Decreases collagen formation
- Increase choleresis
- No toxicity
Case Summary

- Treatment plan:
  - Cyclosporine
  - Ursodial
  - Vitamin E
  - SAMe/Silibin
- Recheck liver enzymes in 1 month

Beau
6 year N/M

Final Key Points

- Know the high risk breeds
- Chronic ALT increases should be investigated
- Most clinical at 6-10 years of age
  (unusual to see old dogs with CH)
- Early diagnosis and therapy improves prognosis
Questions to the Specialist

Please email your questions to solveit@aahanet.org by Sunday, November 6, 2011.

Dr. Twedt will provide written responses to all of the questions and answers will be posted on the Solve It! web pages by Friday, November 18, 2011.

To complete the evaluation, please go to the following website:

http://www.keysurvey.com/survey/391676/1cd7/

Thank you for your participation!