

# IVG Newsletter

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# Canine Chronic Hepatitis

**CANINE CHRONIC HEPATITIS (CH)** is a chronic inflammatory liver disease that without intervention, progresses to hepatocellular necrosis and fibrosis/cirrhosis. A definitive diagnosis is made with histopathology. There are several known causes of canine hepatitis, including infections such as bartonella, helicobacter, leptospirosis and ehrlichia. Exposure to aflatoxins and anticonvulsant medications can cause hepatitis as well.

Many dog breeds have a familial tendency to develop hepatitis, including Doberman Pinschers, Bedlington Terriers, West Highland White Terriers, Cocker Spaniels, Dalmatians, Skye Terriers, Standard Poodles, German Shepard dogs, Labrador Retrievers, Scottish Terriers and Beagles. Some of these breeds such as the Bedlington Terrier have been shown to have defects in copper metabolism, and subsequent copper toxicity that causes hepatitis. Other breeds are suspected to have a variation of this toxicity. However, most cases of CH are idiopathic, where no specific underlying cause can be found.

Cases of apparent acute idiopathic canine hepatitis are treated relatively commonly by veterinarians. These dogs develop typical symptoms of liver disease (lethargy, anorexia, vomiting, diarrhea, polyuria/polydipsia (PUPD), weight loss, etc) along with elevated liver enzymes and an inflamed-appearing liver. Often after a few days of supportive care the dogs appear to recover clinically and their bloodwork is improved, so their liver is never biopsied. Importantly a portion of these dogs may progress, subclinically, to chronic hepatitis. It has been shown that monitoring serum liver enzymes will not likely detect this progression. These dogs become clinical 4 - 8 months later and at this stage have irreversible fibrotic damage to the liver. In one study of 21 dogs with acute hepatitis where acute and repeat liver biopsies were taken in 12 dogs, 5 of them progressed to CH. If the transition from acute hepatitis to CH is detected early, it can be successfully treated with corticosteroids. Therefore, some veterinarians are advocating control biopsies be taken 4 weeks after an episode of acute hepatitis so chronic disease can be detected early.

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## CLINICAL SIGNS

Clinical signs of CH are often inapparent until the disease is relatively advanced and occur most commonly at 4 - 7 years of age. Females may be more affected. Symptoms of severe failure (cirrhosis) include lethargy, anorexia, vomiting, weight loss, PUPD, diarrhea and ascites. Less advanced disease manifests as lethargy, poor appetite, weight loss, with or without vomiting. Some dogs are diagnosed in an early stage when routine screening bloodwork is done, or when lab abnormalities are found when testing for other conditions. Physical exam findings are relatively unremarkable and may include poor body condition, ascites and jaundice. The most common laboratory abnormalities are an elevated ALT (avg 10X), and ALP (avg 5X) though both may be minimally elevated if disease has progressed to cirrhosis. A low albumin and cholesterol are seen 40 - 75% of the time. A high globulin and low BUN may be present. Bile acids are elevated but bilirubin often is not. Hypoglycemia is rare and suggests a very bad prognosis (< 1 week). There may be a mild anemia due to chronic disease. A leukocytosis and consumptive thrombocytopenia may be present. A prolonged PT and PTT are seen 10 - 60% of the time and may suggest a very bad prognosis. An ascites will be a transudate or modified transudate. Radiographs may show ascites or a small liver. Ultrasound findings are often non-specific and the liver may or may not be inhomogenous, iso-, hyper- or hypoechoic with or without nodules, or multiple acquired shunts.

## HISTOPATHOLOGY

The three cornerstones of canine CH found on liver biopsy include inflammation, necrosis and fibrosis, with or without cirrhosis (fig. 2). Excess copper may or may not be found, along with hydropic change and nodular regeneration. Hydropic change is vacuole development due to endogenous steroid release. The inflammation is predominantly lymphoplasmacytic, possibly with some neutrophils and macrophages, but it is not granulomatous. The necrosis is initially piecemeal, meaning affecting hepatocytes adjacent to the portal tract or limiting plate. With time necrosis extends to the central veins, a progression called bridging necrosis. Necrosis leaves behind space (hepatocyte dropout) and the liver responds by producing hepatocytes and bile duct epithelium. However the extracellular matrix is disrupted by inflammatory enzymes and releases substances that attract collagen-producing cells creating an altered, fibroid, matrix on which hepatocytes are growing. Cirrhosis occurs when there are regenerative nodules surrounded by fibrous connective tissue bridging between portal tracts. In a recent study of 101 dogs with hepatitis, 29 had copper levels high enough to suggest copper as an underlying or contributory etiology. Routinely staining liver biopsy samples for copper is recommended. A semi-quantitative assessment of copper levels can be obtained staining with either rubeanic acid or rhodanine stain which stain the copper bright red. Results are reported as mild, moderate or severe, or on a scale such as 1 to 4. Formalin-stained, paraffin embedded samples can be stained for copper, but the samples need to be pretty big: - 3, 14-gauge needle biopsies or a wedge biopsy are preferred. Commercial labs offer a panel of stains for liver pathology that includes Masson's trichrome stain for collagen, prussian blue stain for iron and rhodanine stain for copper. The cost is about \$25.00. Quantitative atomic absorption analysis is done at Colorado State University and the California Animal Health and Food Safety Lab on 1 gram of fresh frozen tissue in a copper-free serum blood tube. There is a 1 - 2 week turnaround at CSU for \$35.00 and 3 - 5 days at California for \$100.00.

## TREATMENT

The goals for treatment of canine CH include reducing inflammation, alleviating the underlying cause when possible, anti-oxidant therapy, reducing or preventing

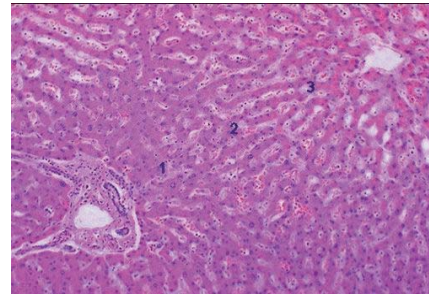


Fig. 1 Normal liver lobules

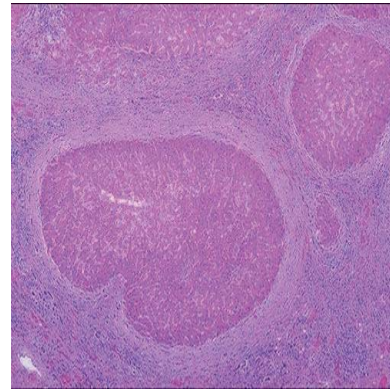


Fig. 2 Chronic Hepatitis Histopathology

fibrosis, treating hepatic encephalopathy and supportive care. Glucocorticoids are the mainstay of therapy. Benefits include being anti-inflammatory, inhibiting fibrosis, stimulating appetite, decreasing intestinal copper absorption, making the patient feel better and prolonging life. Prednisolone or prednisone is used at 2.2 mg/kg/day and tapering after clinical signs and hepatic enzymes improve. ALP will rise or remain elevated but ALT should decline. Azathioprine (Imuran) at 1.0 mg/kg/day may be used if steroids are ineffective or cause excessive side effects. Try to taper to every other day and monitor for liver toxicity and bone marrow suppression. Oxidation is a significant mechanism of hepatic damage. Anti-oxidants work in many ways to prevent oxidative damage and have minimal to no side-effects. Commonly used anti-oxidants include S-adenosyl-methionine (SAM-e) at 18mg/kg daily, Silymarin (Milk Thistle) at 20 - 50 mg/kg daily and vitamin E at 400 - 600 IU daily. No studies of any of these compounds have been carried out to demonstrate efficacy in chronic hepatitis. Ursodeoxycholic Acid (Ursodiol) is a natural, hydrophilic bile acid produced in the liver which is helpful because it is hepatoprotective in many ways including, displacing hydrophobic bile acids that induce apoptosis, modulating the immune system, increasing bile flow and increasing production of anti-oxidants. The dose is 15mg/kg daily and there are virtually no side effects. Many drugs - prednisone, azathioprine, vitamin E, zinc and penicillamine - are known to have preventative, anti-fibrotic effects. Colchicine is a microtubule assembly inhibitor that increases collagenase activity, so may be able to reduce existing fibrosis. The dose is 0.03mg/kg daily. This can uncommonly induce vomiting and diarrhea.

>continued

## Canine Chronic Hepatitis

No studies of efficacy in canine CH have been carried out. To minimize hepatic encephalopathy a diet low in aromatic amino acids such as Hill's L/D is recommended, if it is tolerated. Lactulose and a soluble fiber source also help by decreasing ammonia uptake from the colon by inducing bacteria to produce acids that decrease colonic pH, converting ammonia to ammonium, which cannot be absorbed. Neomycin, 22mg/kg tid to qid, flagyl, 7 – 15 mg/kg bid and clavamox 10 – 15 mg/kg bid decrease the colonic bacterial population that produce ammonia. In treating ascites, lasix should be used cautiously, or not at all, because it can cause hypokalemia and alkalosis. In the alkalotic state there is more ammonia than ammonium and it diffuses across the blood brain barrier readily. With hypokalemia, potassium exits cells and hydrogen ions enter cells causing intracellular acidosis. Ammonia readily enters the cells, becomes ionized, then cannot leave the cell. Use the potassium-sparing aldosterone receptor antagonist diuretic, spironolactone at 2 – 4 mg/kg bid. Additional supportive care includes preventing or treating gastroduodenal ulceration with H-2 receptor blockers, proton pump inhibitors and/or carafate, treating nausea with anti-emetics and giving fluid and colloid support. When hepatitis is induced by copper toxicity, chelation should be instituted with penicillamine at 10 – 15 mg/kg bid for about 3 months. The drug binds extracellular copper and the complex is excreted in urine. Intracellular copper exchanges with extracellular copper and it is eventually removed. Penicillamine causes nausea and vomiting about 30% of the time – this side effect can be diminished by giving it with food. Zinc acetate or zinc gluconate at 5 – 10 mg/kg bid one hour before a meal induces the copper binding protein, metallothionein, in enterocytes. Dietary copper remains in the enterocyte and is eventually sloughed with the cell, therefore zinc can be used to prevent as well as remove existing copper accumulation. Side effects include a transient inappetence and a copper deficiency hemolytic anemia if treatment is over done.

Bedlington Terriers are known to have an autosomal recessive metabolic defect in biliary copper excretion which causes copper to progressively accumulate in the liver causing oxidative damage after reaching about 2,000 ppm. Clinical signs can be silent, can be those of acute or chronic liver failure and can be combined with hemolytic anemia. A diagnosis is made with histopathology and

copper quantification showing excess copper, and subsequent inflammation, necrosis and fibrosis. To screen these dogs, liver biopsies should be performed at 6 and 15 months of age. Unaffected animals have normal copper levels. Heterozygotes initially have high copper levels that taper at the second biopsy. Homozygotes have high copper levels that worsen over time. Affected animals should be removed from the breeding pool. If these animals are treated at a young age, they have a good prognosis. Hepatic copper storage and associated hepatitis seem to be breed associated in several other breeds such as the Doberman Pinscher, West Highland White Terrier, Dalmatian, Skye Terrier, Cocker Spaniel and Labrador Retriever, though the relationship is uncertain. Copper accumulation may be due to a defect in copper metabolism, or may be secondary to altered biliary excretion with cholestatic liver disease. Copper is an element of ingested proteins that is generally ingested in excess, and is eliminated by the liver and biliary system to avoid toxicity. Normal dogs have less than 400 ppm (ug Copper/gm liver). Dogs with hepatic disease with >2,000 ppm copper likely have disease caused by copper toxicity. Less than 1,000 ppm copper suggests copper accumulation secondary to liver disease, and copper between 1,000 and 2,000 ppm may be the primary cause of hepatitis. Median survival for canine CH is 16 – 18 months in three recent studies where there was no distinction between idiopathic and copper-associated disease. Better identification of copper-associated forms of hepatitis may result in an improvement in survival time.



References available upon request

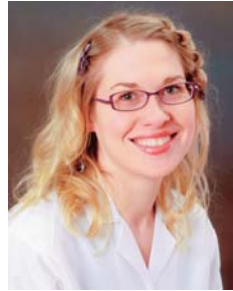
# Test Your Skills: ECG Rounds

**CASE 1:** A 12 year old (15.4 lb) spayed female Shih Tzu was evaluated for two recent episodes of collapse and a 2 week history of decreased activity level. On physical examination, she was quiet, alert and responsive. The heart rate was 40-50 beats/minute with an intermittently irregular rhythm. Thoracic auscultation revealed a grade II/VI left apical systolic murmur. Pulses were strong and synchronous and her lungs were clear bilaterally.

An ECG was obtained to further characterize her arrhythmia. Paper speed @ 50 mm/sec, 10 mm = 1 mv

Question: Interpret the Following ECG

Laura Hatton, DVM, (Practice limited to Cardiology)



Dr. Laura Hatton practices at Massachusetts Veterinary Referral Hospital in Woburn, MA.



**Case 1: The Diagnosis is:** *(see over)*

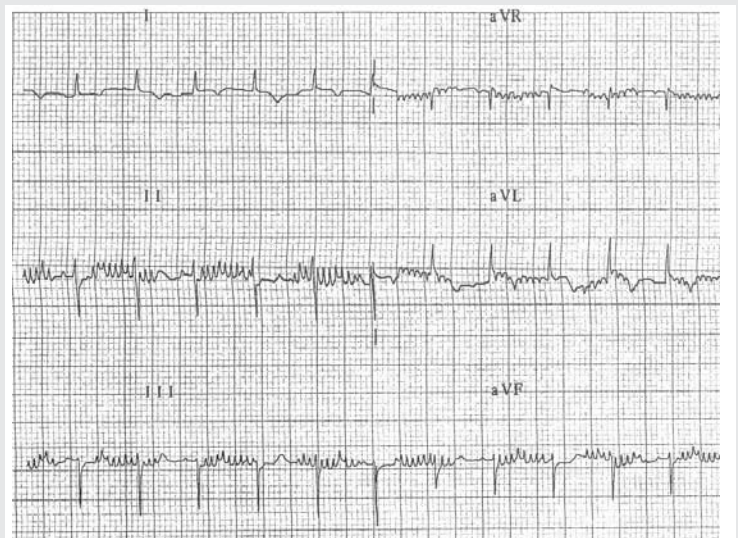
- (a) Sinus rhythm with a right bundle branch block pattern is present
- (b) There is high-grade second degree AV block with a right bundle branch block pattern
- (c) There is third degree AV block with a ventricular escape rhythm
- (d) There is first degree AV block with single monomorphic VPC's.

**CASE 2:** ECG obtained from a 10 year old FS DSH that presented for a routine recheck of previously diagnosed hypertrophic cardiomyopathy and history of prior congestive heart failure. The patient has been doing well at home with no adverse signs or symptoms reported by the owner. Auscultation revealed a heart rate of ~ 150 beats/minute and grade II/VI left parasternal systolic murmur. Femoral pulses were strong and synchronous. The patient was eupneic with clear lung sounds bilaterally. Paper speed @ 25 mm/sec, 10 mm = 1 mv

Question: Interpret the ECG

**Case 2: The Diagnosis is:** *(see over)*

- (a) Atrial fibrillation with ventricular escape beats are present.
- (b) A right bundle branch block is present.
- (c) An artifact is evident in the baseline with a left axis deviation.
- (d) Atrial flutter is present with 4:1 conduction.



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## Test Your Skills: ECG Rounds

Fig. 1: AV Block.

source: Opie, 1998

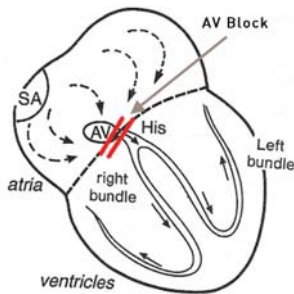


Fig 2: Dog with pacemaker implanted.



### CASE 1: CORRECT ANSWER: C

Third degree AV block is characterized by persistent, complete blockage of electrical impulse conduction from the atria to the ventricles (fig. 1). Electrocardiographically, P waves occur regularly and at a normal or elevated rate, but are not followed by QRS complexes. Ventricular activity consists of QRS complexes that occur regularly but at a very slow rate (ventricular escape rhythm) and are often wide and bizarre in morphology.

Third degree AV block is more common in older animals, but can occur at any age. Patients may present for syncope, episodic or persistent lethargy or weakness with or without signs of concurrent CHF (tachypnea, dyspnea, abdominal distension).

Physical exam findings reveal bradycardia (HR typically < 50 beats/minute in dogs, < 120 beats/minute in cats).

Intermittent jugular pulsations called "cannon a waves" may be present, that are caused by intermittent right atrial contraction against a closed tricuspid valve. The first heart sound may vary in intensity secondary to variability in the end-diastolic ventricular volume. Some animals will also have signs of low-output failure (i.e. forward heart failure), or congestive heart failure.

Causes of third degree AV block include any abnormality which leads to failure of supraventricular impulses through the AV junction. Causes include idiopathic fibrosis of the AV node (most common reason), primary cardiomyopathies (e.g. HCM), infiltrative disease of the AV node (e.g. neoplasia or amyloidosis), certain congenital heart defects (e.g. VSD or aortic stenosis), bacterial endocarditis, myocardial infarction, excessive vagal tone, hypothyroidism, infection (e.g.

*Trypanosoma cruzi* [Chagas disease], *B. burgdorferi*-associated myocarditis), severe hyperkalemia, or iatrogenically via cardiac medications (e.g.  $\beta$ -blockers, calcium channel blockers, digitalis).

In addition to an ECG the initial database may include an echocardiogram to rule out any structural intracardiac causes with or without incidental findings of other abnormalities (e.g. valvular endocardiosis is common); thoracic radiographs to rule out congestive heart failure and other intrathoracic abnormalities, and complete bloodwork – complete blood count, serum biochemistry profile, and urinalysis (unremarkable unless concurrent disease conditions are present).

The goals of treatment are to restore normal cardiac output and/or resolve CHF if it is present.

Acute general treatment consists of temporary, and/or permanent, artificial pacemaker implantation.

IV positive chronotropic medications (e.g. can be administered) however, response is variable and almost always unrewarding with third degree AV block. Chronic treatment requires permanent artificial pacemaker implantation.

Prognosis is good after successful pacemaker implantation (better if CHF has not been present). We currently perform multiple types of interventional procedures at Mass Vet, including pacemaker implantation (fig. 2).

### CASE 1 ECG (REFER TO PAGE 5)

Third degree AV block is due to failure of the AV junction (AV node and bundle of His, fig.1), to conduct supraventricular electrical impulses distal to the site of interruption.

Ventricular depolarization (and contraction) occurs due to the development of an "escape rhythm" that emanates from the pacemaker cells either in the more distal part of the AV junction (the His bundle) or the ventricles.

The result is a faster atrial rate (P waves = orange circles) and slower ventricular rate (QRS complexes = green squares) that occur independently of one another (see page 5). With an escape rhythm the QRS complexes may appear wide and bizarre, or normal, presumably, arising from ventricles or from lower AV junction. The HR will be 30-70 bpm in dogs vs. 70-140 beats/minute in cats. In this ECG tracing the atrial rate is approx. 158 beats/minute, while the ventricular rate is approx. 50 beats/minute.

## CASE 2: CORRECT ANSWER: C

This patient was purring which created artificial interference in the baseline in all but lead I. In addition, a left axis deviation (aka left anterior fascicular block) is present.

Electrical artifacts in the ECG may be external or internal. External artifacts introduced by line current (50-60 Hz) may be minimized by straightening the lead wires so that they are aligned with the patient's body. Internal artifacts may result from muscle tremors, shivering, hiccups, or other factors, producing a "noisy baseline".

Tremor or trembling is another common artifact on ECGs from dogs and cats. Panting can make the baseline undulate at the frequency of the respiratory rate, and a cat's purring may create an underlying undulating baseline as seen above. Switching leads while still recording produces a period during which the baseline is flat that can mimic sinus arrest. Brief deflections, often created by someone touching the electrode or a patient jerking a limb, can mimic ventricular premature contractions. Artifacts can usually be distinguished from VPCs by the fact that they do not have a large, bizarre T wave following them.

## ARTIFACTS CAN BE MINIMIZED BY:

- Using enough isopropyl alcohol at the point of contact between the skin clips and the skin.
- Avoiding metal-on-metal contact between clips (often with smaller dogs and cats), the wires need to be held apart by the person performing the ECG to avoid wire-to-wire or clip-to-clip contact during the procedure.
- Choosing a quiet, comfortable environment to perform the ECG; a cold or stressful environment may trigger shivering (excess motion artifact), whereas an excessively warm or stressful environment can induce panting in dogs (and motion artifact).
- Evaluating multiple ECG leads rather than just one lead; each lead provides a different prospective on the electrical activity of the heart. Lead II is not necessarily the lead in which the clearest P waves, QRS complexes, and T waves, or minimal artifact are seen.
- Motion artifact may mimic abnormal cardiac activity and cause misdiagnosis.

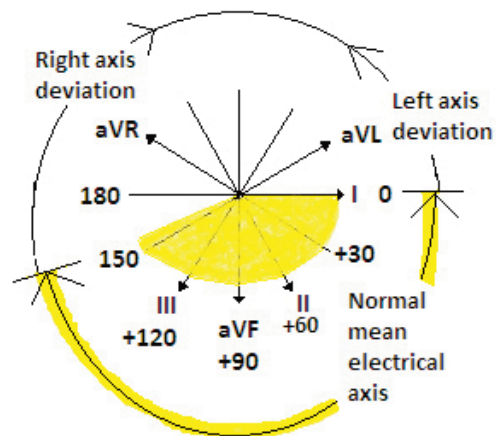


Fig. 1: Normal mean electrical axis in a cat (yellow shaded area) with left and right axis deviations.

## LEFT AXIS DEVIATION

A left axis shift or deviation (LAD) is a shift of the mean electrical axis cranially and to the left, without an increase in QRS complex duration. The exact boundaries of a left axis shift are uncertain in dogs and cats. It certainly is less than +40 degrees in the dog and less than 0 degrees in the cat, but exactly where this definition ends is unknown.

A left axis shift without an increase in QRS complex duration is commonly called a left anterior fascicular block (LAFB) or left anterior hemiblock. These terms originate from a historic belief that the left bundle branch divided into two minor branches, or fascicles. This is anatomically incorrect, as no such fascicles exist in dogs, cats, or humans.

LAFB is common in people without overt cardiac disease, as well as those with a wide range of diseases, including coronary artery disease, myocardial infarction (especially occlusion of the left anterior descending coronary artery), left ventricular hypertrophy, hypertrophic and dilated cardiomyopathy, and various cardiac degenerative diseases.

A marked left axis deviation in cats (referred to as LAFB by some) is often seen with cats that have hypertrophic cardiomyopathy, but can also be seen in normal cats. Therefore, it is important to recognize this pattern of left axis deviation (tall R wave in leads I and aVL, S wave present in leads II, III, and aVF), although the name of left anterior fascicular block is technically not appropriate. If a left axis deviation is observed on ECG then an appropriate next step would be to obtain an echocardiogram to rule out potential HCM.





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