A liver biopsy is a chance to tailor your patients treatment in order to maximize successful response.

Assessing liver enzyme elevations are valuable but do not provide a definitive diagnosis. Furthermore, canine copper storage studies have shown that ALT elevations are not always that sensitive despite significant copper accumulation. In fact, the same general rule applies to cats. ALT is not always a very sensitive indicator of hepatic injury. Copper hepatopathy is high on our radar for Bedlingtons, Labradors, Dobermans, Dalmatians and West Highland White Terriers.

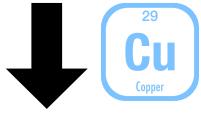
We do have genetic testing available to guide our index of suspicion in Labradors, Labradoodles and Dobermans but this disease can be found in other historically non-predisposed breeds and is on rise. It has even been seen in a young French Bulldog with concurrent microvascular dysplasia - as if we needed to add another concern to their long list!

Consider our Labrador patient with an ALT of 437. It is not possible to know if there is copper storage disease, evidence of immune mediated disease or idiopathic chronic hepatitis with bridging fibrosis, without a biopsy. Bile acids will provide additional important information but normal values do not negate the need for a biopsy to direct therapy.

Each of these aforementioned diseases require specific management for success. Prognosis and long term medication and nutrition management expectations will vary based on diagnosis and severity.

How might treatment change depending on a biopsy?

Copper Associated Hepatopathy: Knowing whether it is imperative to use a copper restricted veterinary prescription diet (currently limited options on the market) or a nutritionist formulated diet is going to depend on the copper identified by staining and quantitative analysis. Not all liver diseases require protein restriction or copper restriction! In addition, dietary copper restriction is not going to be sufficient in certain cases.

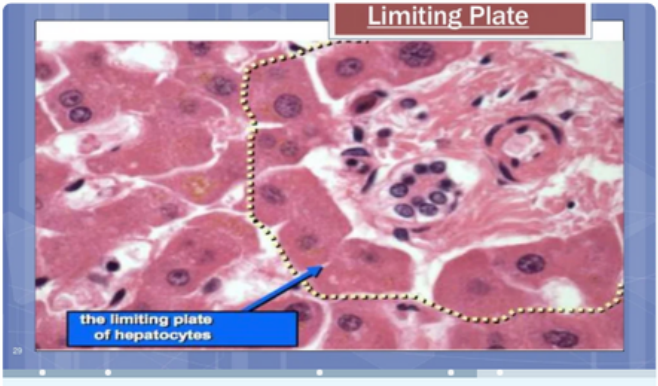


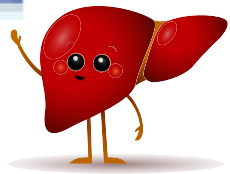
Oral copper chelation therapy will be needed for success when copper levels are in the toxic range. This treatment is expensive and can have side effects as such we don't reach for these drugs without having adequate information.

Canine Immune Mediated Hepatitis: We are still defining the criteria for definitive diagnosis but there are features the pathologist will look for on your biopsy. Why should we try to make this distinction? Canine immune mediated hepatitis requires long term immunosuppressive therapy. **Lifetime therapy** at the lowest effective dose is advised given the high risk of relapse seen in dogs as in people.

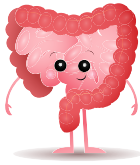
Given longterm therapy needs, it may be best for your patient to reach for cyclosporine over prednisone. Without a biopsy it will be difficult to move forward with confidence to potential other immunosuppressive therapies if the response to initial treatment is not as expected.

Arriving at a working diagnosis of immune mediated disease will include noting the breed/family history, being female, ruling out other causes (e.g. copper, infectious agent, drug or toxin), and noting a hepatocellular hepatopathy with a predominantly lymphocytic infiltrate. It is also recommended to look for interface hepatitis. This may be a clue for canine medicine as it is an important feature of human patients with autoimmune hepatitis. **Interface hepatitis means liver cells are injured or dying at the limiting plate** (invisible border around a portal triad) as well as seeing inflammation extending out into the surrounding periportal tissue.



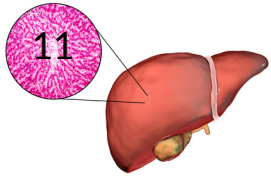


Reactive Hepatopathy: Liver enzyme elevations are generally mild and in theory bile acids are normal. The key features of this disease is the **lack** of individual hepatocyte death, no fibrosis and generally mild inflammation confined within portal tracts. This will guide you to focus on treatment outside the liver and pay specific attention to the GI tract.



Fibrosis (scar/connective tissue) within the liver is going to be prognostic. Special stains are used to delineate the connective tissue. There are variable patterns but bridging fibrosis from portal to central regions and especially dissecting fibrosis will be associated with a worse prognosis.

MULTIPLE surgical wedge or laparoscopic cup biopsies are the best chance to provide sufficient hepatic architecture for the pathologist to provide an accurate diagnosis. This is particularly true in congenital, inflammatory or copper associated diseases where there is **considerable variation in pathology between liver lobes**. One goal is to have 11 portal triads as a minimum but preferably 12-15. Avoid taking surgical biopsies from the extreme edge of the liver as it may not be representative of the true underlying pathology. If surgery or laparoscopy is not an option, 14-16 G percutaneous ultrasound-guided biopsies, if performed correctly, can provide adequate specimens. To achieve the ideal number of portal triads one needs 2-4 laparscopic cup biopsies and > 4 needle biopsies.



Aspirates or single biospies can be useful for diffuse diseases (lymphoma, fatty liver) but can miss concurrent conditions. Consider this piece of trivia. In a 35kg dog, a single needle biopsy represents **1/60,000th** of the entire liver!

For **copper** -Approximately 20-40 mg of liver (wet weight) are required for copper quantitation using atomic absorption spectrometry. This amount equates to 1 full 14 G (2-cm long) needle biopsy specimen or half of a 5-mm laparoscopic biopsy specimen. A full length 18 G needle biopsy provides only 3-5 mg of liver tissue and copper measurement will be erroneously low. Discordant copper measurements and copper staining may occur due to fibrosis in the copper dedicated biopsy.

Anaerobic and aerobic liver **cultures** should be obtained as part of a complete investigation.

Plan ahead to **minimize patient risk** for bleeding as well as provide adequate post procedure monitoring with the guidelines available in the ACVIM open access consensus statement on canine chronic hepatitis.

Lastly, ask yourself if your **history** is complete prior to sample submission. The pathologist needs your input to provide clinically relevant comments in relation to the what they see under the scope.

TRUE NORTH
VETERINARY DIAGNOSTICS

References:

Webster CRL, Center SA, Cullen JM, et al. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. J Vet Intern Med. 2019;33(3):1173-1200. doi:10.1111/jvim.15467

Reece J, Pavlick M, Penninck DG, Webster CRL. Hemorrhage and complications associated with percutaneous ultrasound guided liver biopsy in dogs. J Vet Intern Med. 2020;34(6):2398-2404. doi:10.1111/jvim.15942

Favier RP, Spee B, Schotanus BA, van den Ingh TS, Fieten H, Brinkhof B, Viebahn CS, Penning LC, Rothuizen J. COMMD1-deficient dogs accumulate copper in hepatocytes and provide a good model for chronic hepatitis and fibrosis. PLoS One. 2012;7(8):e42158. doi: 10.1371/journal.pone.0042158. Epub 2012 Aug 6. PMID: 22879914; PMCID: PMC3412840.

Pindar S, Ramirez C. Predicting copper toxicosis: relationship between the ATP7A and ATP7B gene mutations and hepatic copper quantification in dogs. Hum Genet. 2019 May;138(5):541-546. doi: 10.1007/s00439-019-02010-y. Epub 2019 May 6. PMID: 31062085.

Strickland JM, Buchweitz JP, Smedley RC, et al. Hepatic copper concentrations in 546 dogs (1982-2015). J Vet Intern Med. 2018;32(6):1943-1950. doi:10.1111/jvim.15308