**Update Anaphylaxis and The Use of the Gallbladder Halo Sign**

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**Introduction:**

The diagnosis of Anaphylaxis (AX) is problematic in human and veterinary medicine (see below and the reluctance to give epinephrine). This lecture will review traditional ways in diagnosing AX as well as additional supportive evidence of gallbladder wall edema, referred to as the “Gallbladder Halo Sign.” Importantly, AX-related gallbladder wall swelling is a dog condition because their shock organ, highest concentration of mast cells, is in their liver and GI tract vs. humans and cats, in which their shock organ is the lung. **Key Point:** Traditional ways to diagnose AX have included (1-3) 1) History of recent drug administration, vaccine administration, witnessed Hymenoptera sting(s) 2) Acute gastrointestinal signs followed by weakness and collapse 3) Lab findings of hemocoagulation and increased liver enzymes (ALT, AST) and more recently the addition of 4) *The observation of sonographically-detected gallbladder wall edema, referred to as the “Gallbladder Halo Sign” (Quantz, et al. JVECC 2009). *A clinical feature of AX that aids in its diagnosis but is not pathognomonic.

The sonographic issue is not the use of the “gallbladder wall halo sign” for a diagnosis in dogs with obvious allergic hypersensitivity reactions based on history, including recent drug or vaccine administration, witnessed Hymenoptera sting(s); or dogs that have on physical examination combinations of pruritic angioedema of the muzzle, thickening of the pinna, and periocular swelling and/or urticaria. The problem occurs with diagnostic use and proper interpretation as to cause of gallbladder wall edema when observed in the collapsed or weak dog without a supportive history of AX; or physical exam signs consistent with an allergic hypersensitivity reaction. In fact, Quantz et al. reported that only 60% of dogs with AX have cutaneous signs, 40% don’t. **In our experience the frequency is more like 95% of dogs with AX have no cutaneous sign!** These dogs are often triaged and have AFAST™/TFAST™ performed as part of initial patient assessment; thus, when the “gallbladder halo sign” is observed in these dogs it is imperative the attending veterinarian understand that there are other important causes for gallbladder wall edema and that its observation is NOT pathognomonic for AX (see Table)! **Key Point:** Most dogs with AX do NOT have cutaneous signs or witnessed Hymenoptera sting(s).

Veterinarians should know to consider and rule out the diagnosis of not only AX, but also pericardial effusion/tamponade, right-sided congestive heart failure, and generalized systolic cardiac dysfunction (Dilated Cardiomyopathy [DCM]). The attending veterinarian should resist satisfaction of search error through the abbreviated ultrasound exam of a Focused Gallbladder because mistakes will be made. It is important for the sonographer to habitually complete AFAST™/TFAST™ so that a mis-diagnosis of AX for pericardial effusion, right-sided congestive heart failure, generalized systolic cardiac dysfunction (e.g., DCM) does not occur. There are also other causes of gallbladder wall edema of which veterinarians should be familiar that generally do not present with acute weakness of collapse (see Table below). **Key Point:** Gallbladder wall edema, the “gallbladder halo sign” is NOT pathognomonic for AX. Pericardial effusion, right-sided congestive heart failure, and generalized systolic heart failure (DCM), should be ruled out before the administration of large volumes of intravenous fluids.

Equally as important, dogs with AX commonly have some degree of free fluid in their abdominal cavity (positive AFS, see AFAST™ Proceedings). Most often these dogs are AFS 1 with small amount of untappable inaccessible free fluid at their DH View. However, in higher-scoring AFS 3 and AFS 4 dogs
having free fluid that is safely accessible via abdominocentesis, the ascites is most commonly characterized as a hemorrhagic effusions with the abdominal fluid PCV (packed cell volume) at least 50% of the peripheral blood PCV (Lisciandro, JVECC, Abstract 2016). Veterinarians need to know that canine AX potentially carries with it the complication of a medically treated, AX-induced heparin-related hemoabdomen because operating on this patient will likely be fatal. **Key Point: AX-induced heparin-related hemoabdomen is a common finding and medically treated. Failure to recognize this canine AX complication is likely fatal if you take this patient to surgery.**

**Use of AFAST³/TFAST³:**

The target-organ approach of AFAST and its AFAST-applied fluid scoring system, the FAST DH View, and the TFAST format that also assesses heart and lung, encourages the sonographer using these abbreviated formats to look beyond the simplified objectives by some teachings of FAST as being merely a flash exam with a fluid-positive or fluid-negative endpoint. The Global FAST (GFAST) approach using these 3 formats (AFAST, TFAST and Vet BLUE) carries a much more cerebral mindset taking advantage of structures viewed during GFAST that provide important clinical information and helping favorably direct patient care.

**The Sonographic Evaluation of the Gallbladder**

A classic example is the observation of the gallbladder at the FAST DH View (part of both the AFAST³ and TFAST³ formats). The gallbladder is fluid-filled and thus easily recognized by the non-radiologist sonographer; and is reliably imaged in dogs and cats at the FAST DH View when placed in right lateral recumbency. There are 3 major features to consider when viewing the gallbladder including its shape, lumen contents and its wall.

**The Diaphragmatico-Hepatic (DH) View**

In normalcy, the gallbladder sonographically is generally oval in longitudinal (sagittal) orientation with a lumen that is homogeneously anechoic (black); however, exceptions exist, and dogs and more commonly cats may have bi-lobed (oddly-shaped) gallbladders; and in dogs the gallbladder lumen may have echogenic (gray) material, referred to as sludge, that may also be considered normal effusions.


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when placed into clinical context. On the other hand, the gallbladder wall is quite reliably a thin hyperechoic (white) line in both the canine and the feline species despite being reported to be considered as normal up to a thickness of 2-3 mm. In summary, the sonographic features of the canine and feline gallbladder are easy to appreciate by non-radiologist sonographers during both AFAST³ and TFAST³ at the DH View.

Image showing the normal gallbladder wall as a thin hyperechoic (white) line at the FAST³ DH View.

Compare to gallbladder wall edema referred to as the “Gallbladder Halo Sign” in subsequent images.

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In 2009, Quantz et al. performed a landmark study that correlated the presence of a thickened gallbladder wall, referred to as the gallbladder halo sign, with anaphylaxis (AX) in dogs because their shock organ is the gastro-intestinal tract and liver. In contrast, the shock organ of cats and humans is the lung (thus neither humans nor cats get an AX-induced gallbladder halo sign). In previous AX research using canine research models, the sonographic finding of the gallbladder wall thickening was noted but had never been applied clinically. What Quantz et al. found was that when dogs experience AX, the massive release of histamine causes the hepatic sphincters to tighten resulting in massive hepatic venous congestion that causes gallbladder wall edema within minutes. The gallbladder wall edema is easily recognized sonographically by its hyperechoic (white) inner and outer walls with a sonolucent line (typically anechoic [black]) in between. In other words, the gallbladder wall becomes layered as white, black, and white; and thus dubbed the “gallbladder halo sign.” Moreover, Quantz et al. found that the gallbladder halo sign was not only sensitive and specific for AX, but also an immediate finding, in contrast to the delay of the spike of the historical marker of serum alanine transaminase (ALT), which may take 2-4 hours.

Varying degrees of gallbladder wall edema referred to as the “Gallbladder Halo Sign” in different dogs with anaphylaxis at the FAST³ DH View. A) mild B) severe. We have found the degree of gallbladder wall edema inconsistently correlates with severity of AX.

Note the sonographic layering of white, black and white of lumen wall, its sonolucent center, and outer wall respectively. Compare to normal thin hyperechoic (white) line in previous image.

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Modified from Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley ©2014 with the sonographic layering placed as white, black and white. Compare to previous unlabeled image.

GB: gallbladder; LIV: liver; DIA: diaphragm

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Importantly, it should be noted that the diagnosis of AX in human patients is problematic because there is no good rapid test for diagnosis, and serum markers (tryptase, PAF, histamine) are not immediately available when clinical decisions, e.g., the administration of epinephrine (EPI), are being made by attending physicians. As a result, it has been reported that up to 57% of AX cases are misdiagnosed in the emergency department. Furthermore, one study found that only 14% of human with anaphylaxis deaths were treated with EPI prior to cardiopulmonary arrest; and only 62% received EPI overall (EPI given at time of CPR). The reluctance in giving EPI lies in the myth that EPI can cause fatal reactions in and of itself; so both physicians (fail to administer up to 80% of the time) and veterinarians (unknown % of time) are over-cautious in EPI administration. However, it has been discussed more recently in human medicine that the levels of EPI given through administration of standard doses are 1/20th the toxic levels and thus benefit greatly outweighs risk.

### Causes of Gallbladder Wall Edema (the Gallbladder Halo Sign)

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Anaphylaxis (acute collapse, flat caudal vena cava) – massive histamine release results in hepatic venous congestion</td>
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<tr>
<td>Right-sided heart failure/dysfunction (collapse, weakness, FAT caudal vena cava) – backflow of blood flow from the right heart results in hepatic venous congestion</td>
</tr>
<tr>
<td>Pericardial effusion (acute collapse, weakness, FAT caudal vena cava) – obstruction of blood flow to the right heart results in hepatic venous congestion</td>
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<tr>
<td>Cholecystitis</td>
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<tr>
<td>Pancreatitis</td>
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<td>Hypoalbuminemia, 3rd Spacing</td>
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<tr>
<td>Right-sided volume fluid overload (iatrogenic)</td>
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<tr>
<td>Immune-mediated Hemolytic Anemia (IMHA), unknown cause, speculate immune-mediated</td>
</tr>
<tr>
<td>Post-Blood Transfusion, unknown pathogenesis, speculate immune-mediated</td>
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</tbody>
</table>

Veterinarians should be made aware of the use of the gallbladder halo sign as supportive evidence for the diagnosis of AX in dogs but also be aware of the other causes for gallbladder wall edema. Hasty diagnosis of AX and treatment with EPI, large volumes of crystalloids, and histamine (H1 and H2) blockers and glucocorticoids may not be in the best interest the patient if misdiagnosed. Other potential causes of the gallbladder halo sign include right-sided heart failure, generalized systolic heart failure, pericardial effusion and tamponade, volume overload, 3rd spacing from hypoalbuminemia and vasculitis, primary gallbladder disease, and pancreatitis. By competing AFAST3/TFAST3 mistakes are less likely because the sonographer will automatically be surveying the heart for pericardial effusion, right-sided heart dysfunction failure, and generalized systolic dysfunction (DCM).

The Gallbladder Halo Sign and FAT (distended) CVC in a dog with pericardial effusion (PCE). PCE should be ruled out in collapsed, weak dogs suspected of having AX.

LV: left ventricle; RV: right ventricle; PCE: pericardial effusion; DIA: diaphragm; GB: gallbladder; CVC: caudal vena cava; FF: free abdominal fluid.

Regarding right-sided heart failure/conditions including right-sided heart disease (valvular, functional, obstructive [PHT, PTE]), pericardial effusion with and without cardiac tamponade, and right-sided volume overload (overzealous fluid administration), resultant backflow causes venous congestion of the caudal vena cava (distended caudal vena cava, referred to as FAT) and the hepatic venous system (Tree trunk Sign [Lisciandro, Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley © 2014]). The venous congestion of both the caudal vena cava and the hepatic venous system is obvious sonographically; and gallbladder wall edema is a secondary consequence (Nelson et al., VRUS 2010).

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The phenomenon occurs in humans (and dogs) and has been termed the “cardiac gallbladder” (Lisciandro, unpublished). To the author’s knowledge, the characterization of the caudal vena cava and hepatic venous distension holds true in cats as in dogs and humans: however, the “cardiac gallbladder” phenomenon rarely occurs in cats (the author has had one feline case) and as previously stated, cats do not get AX-induced gallbladder wall swelling as do dogs.

In normalcy, the hepatic veins of dogs and cats are not readily apparent when fanning through the FAST™ DH view. When hepatic venous congestion is suspected (the Tree trunk Sign) by the sonographer, then right-sided heart problems (look at the heart via the FAST™ DH view, and add-on TFAST Pericardial Views) should be investigated (rule out pericardial effusion, right-sided dysfunction/failure, generalized systolic heart dysfunction/failure) as well as consider volume overload in dogs and cats on fluid therapy. Moreover, the use of the dynamic characterization of caudal vena cava (FAT, flat or bounce) is invaluable for sorting out dogs with weakness and collapse. Consider a dog (or cat) with AX, the caudal vena cava will be “flat” due to lack of venous return from profound hypovolemic/distributive shock. In contrast, consider a dog collapsed from pericardial effusion and tamponade, right-sided heart dysfunction/failure, generalized heart dysfunction/failure, the caudal vena cava will be “FAT” from the obstruction of blood flow from the liver to the right atrium. The caudal vena cava characterization is diametrically opposed in these to conditions that can have very similar clinical presentations (the collapsed or weak dog).

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Lastly, dogs with anaphylaxis not uncommonly develop degrees of coagulopathic hemoabdomen, typically abdominal fluid scores (AFS) of 1 or 2, but may have higher scores of AFS 3 and 4. Treatment consists of correcting the coagulopathy with transfusion, e.g., fresh frozen plasma and very rarely red blood cells. Monitoring of the degree of hemorrhage, its worsening, and its resolution, can be done with serial AFS. Most lower-scoring AFS 1 and 2 dogs have normal clotting times and their AFS will return to 0 (negative) within 24-hours. Even dogs with high-scoring AFS 3 and 4 can self resolve without fresh frozen plasma.

It’s important to recognize the complication, and not over-react in stable patients with normal to relatively normal clotting times (<25% over baseline) since many will self resolve within 24-hours (and even some with abnormal coagulation profiles will still resolve without transfusion products); and not unknowingly take an AX-coagulopathic hemoabdomen to surgery, which could be catastrophic for the dog resulting in death (Lisciandro, unpublished). Perplexingly, these cases are difficult to sort out because many dogs have minimal changes in traditional coagulation times (PT, aPTT < 25% above baseline), yet have a high AFS (3,4). The author speculates that the pathogenesis is a combination of mast cell release of heparin and tryptase (some dogs do indeed have discordant PT and aPTT with the aPTT much higher as would occur with heparinization; however, other dogs do not), and the acute hepatic

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venous congestion resulting in the diapedesis of blood and plasma. Findings on exploratory surgery will involve a large swollen (rounded, blunted hepatic lobe edges), oozing, liver and a hemorrhagic effusion (and the dog will unlikely survive [approx 100% death] the surgery, unpublished, Lisciandro 2014).

References: