The Gallbladder Halo Sign: More than Canine Anaphylaxis & Hemoabdomen - a Canine Complication You MUST Know

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Introduction
The lecture will not cover detail regarding the pathophysiology of anaphylaxis of which there exist many excellent published descriptions. Rather, the lecture will focus on how to rapidly gain supportive evidence for the diagnosis of canine anaphylaxis caused by a witnessed or unwitnessed single bee sting (or similar inciting envenomation), including the sonographic marker of gallbladder wall edema; and important rule outs for sonographically-detected gallbladder wall edema that can confound the diagnosis at the expense of the patient; and a newly described fascinating complication referred to by the author as canine “anaphylaxis-related, heparin-induced hemoabdomen” that is medically-treated. The major reason for this lecture is that many veterinarians are now using point-of-care ultrasound, specifically FAST exams, as a life-saving first line, screening test. As a result, ultrasound detects free-fluid and other soft tissue changes that are not recognized without ultrasound; and many triaged collapsed dogs with anaphylaxis have no cutaneous signs nor witnessed inciting envenomation. The focus of the source of anaphylaxis in this lecture disregards the obvious canine with classic cutaneous signs of angioedema, pruritus and urticaria, but focuses on the single Hymenoptera envenomation that is often unwitnessed. All veterinarians need to recognize the strengths and limitations of sonographically-detected gallbladder wall edema, the so-called "halo sign" or "halo effect" or "double rim effect"since its presence is not pathognomonic; and that AX-related, heparin-induced hemoabdomen is a medically-treated canine complication. Without this knowledge, gallbladder wall edema will potentially be misinterpreted and surgical intervention will likely lead to a fatal exploratory surgery with the findings of hepatic swelling, intra-abdominal blood, and non-specific histopathology (Lisciandro JVECC 2016 [Abstract]).

The FAST Diaphragmatico-Hepatic (DH) View
Imaging the Gallbladder and Detecting Intramural Edema
In normalcy, the gallbladder sonographically is generally oval in longitudinal (sagittal) orientation with a lumen that is homogeneously anechoic (black). The gallbladder wall is quite reliably and seen sonographically as a thin hyperechoic (white) line in both canines and felines despite normal thickness reported to be up to 2-3 mm. In summary, the sonographic features of the canine and feline gallbladder, when intramural edema is present, are easy to appreciate by non-radiologist sonographers when imaging the FAST diaphragmatico-hepatic (DH) view (subxiphoid). In a 2009 study, Quantz et al. published in JVECC a brilliant study that correlated the presence of a thickened, edematous, sonographically striated gallbladder wall, referred to as the "gallbladder halo sign" or "halo effect" or "double rim effect", with canine anaphylaxis (AX). Their study design was a result of recognizing that in a canine AX research model, gallbladder wall edema, sonographic striation, was commonly and reliably present. Their oversight in hindsight, was by performing only a focused gallbladder examination (and not AFAST and an abdominal fluid score [better a Global FAST Approach]), thus they likely missed a serious complication.
Figure. Normal expected sonographic appearance of the gallbladder wall in canines (and felines) as a thin white (hyperechoic) line. Unlabeled middle figure labeled with A and B. A shows more subtle gallbladder wall sonographic striation/intramural edema as white (outer wall)-black (intramural)-white (inner wall) or in ultrasound terms as hyperechoic (outer wall)-anechoic (intramural)-hyperechoic (inner wall); and in B shows more obvious/severe gallbladder wall sonographic striation/intramural edema following the same described pattern as in A (white-black-white). Far right image labeled A and B is the same image but now outlined to better show the sonographic striation. *This material is reproduced and modified with permission of John Wiley & Sons, Inc, Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley ©2014*

**Gallbladder Wall Edema as a Sonographic Marker for Canine Anaphylaxis (AX)**

Anaphylactic (AX)-related gallbladder edema is specific to canines because their shock organ, where the highest concentration of mast cells are located, is their liver and gastrointestinal tract. In contrast, the shock organ of cats and people is the lung, thus gallbladder wall edema is not a hallmark of AX in these species. The cause of gallbladder wall edema is the result of massive histamine release causing hepatic venous sphincter constriction and massive generalized hepatic venous congestion. Simply put, when the liver swells, so does the gallbladder wall. This is important to remember when considering other rule outs for canine gallbladder wall edema including gallbladder wall edema associated with hepatic venous congestion from right-sided congestive heart failure. The AX-related intramural gallbladder edema is recognized sonographically as sonographic striation. This sonographic striation appear as a hyperechoic (white) lines representing the inner and outer aspects of the gallbladder wall, and a sonolucent anechoic (black) line striation representing the intramural gallbladder edema. In other words, the gallbladder wall becomes layered as white, black, and white, (sometimes it is white, gray, white), and thus has been dubbed the “gallbladder halo sign” and also less commonly the “halo effect” and “double rim effect.” The Quantz et al. study documented that AX-induced gallbladder edema is an immediate occurrence within seconds/minutes that generally lasts up to 24-48 hours post-insult. Conversely, dogs with mild reactions in the Quantz et al. study were unlikely to have intramural gallbladder wall edema.

**Serum Alanine Transaminase (ALT) as a Serum Marker for Canine Anaphylaxis (AX)**

Because the liver and gastrointestinal tract are the shock organs for the canine species, traditionally serum alanine transaminase (ALT) has been used as supportive evidence for canine AX. However, in the Quantz et al. study, it was stated that serum ALT marker was not as immediate as the occurrence of gallbladder wall edema; and that the ALT may not spike in value for up to 2-4 hours post-insult. Quantz et al. documented a mean ALT of ~ 400 IU/L in anaphylactic dogs in their case study population.

**The Classic Constellations of Signs for Canine Anaphylaxis**

Keeping in mind the canine shock organ, traditional means of diagnosing canine AX have relied on a history of acute collapse in a previously healthy dog. The acute collapse in the otherwise healthy dog is commonly associated with gastrointestinal signs, i.e. vomiting and defecation. The great majority of these dogs have no obvious cutaneous signs (Quantz et al. stated “~40% no cutaneous signs vs. the author's experience is ~95%). Upon presentation due to massive fluid shifts (up to 35% of intravascular volume moved to interstitial compartment in a canine AX research model) caused by histamine release and likely other factors that increase vascular permeability (heparin, bradykinin, histamine-2, platelet activating factor, tryptase), dogs with AX are commonly hemoconcentrated with packed cell volumes (PCV) > 55% range and even higher (in contrast dogs with a hemoabdomen from a bleeding tumor are generally not hemoconcentrated and often low normal PCV or anemic). As previously mentioned, the serum ALT is likewise a marker because of the hepatic insult due to the liver and gastrointestinal tract being the shock organ. The weather should also be considered because many warm days and cool nights make Hymenoptera species lethargic and less likely to move away from the dog walking and sniffing in the grass during these cool evenings and mornings (author’s experience) in spring and fall in San Antonio, Texas.

**Gallbladder Wall Edema is Not Pathognomonic for Canine Anaphylaxis - It’s also a “Cardiac Gallbladder”**

In the collapsed or acutely weak hypotensive canine triaged with the finding of gallbladder wall sonographic striation/edema, other important rule outs relate to the heart and include pericardial effusion, right-sided heart and generalized systolic dysfunction (DCM)(Liscandro unpublished data 2014). The pathophysiology of gallbladder wall edema in these cases is mechanical obstruction of blood flow to the right atrium, in which backflow of blood leads to a distended caudal vena cava (CVC), and subsequent hepatic venous congestion. Simply put, when the liver swells, so does the gallbladder. These rule outs are addressed by looking past the diaphragm at the FAST DH view for pericardial effusion, the
classic "racetrack sign" of pericardial effusion rounding the muscular apex of the heart; and adding the right TFAST PeriCardial (PCS) view to assess contractility at the left ventricular short-axis view. Moreover, the really savvy sonographer always, always looks at the caudal vena cava (CVC) where it traverses the diaphragm while at the FAST DH view. The CVC is a marker for central venous pressure (CVP) and its human counterpart, the inferior vena cava at the analogous location, is ubiquitously being taught to medical doctors. The CVC in AX is flat (no volume, low CVP) with no variation (< 10%) in its diameter (< 5 mm) vs. the CVC characterization in pericardial effusion and cardiac cases is diametrically opposed as FAT (too much volume, high CVP), or distended with minimal variation (< 10%) in it diameter (> 1 cm). When the CVC is FAT from a high CVP, hepatic veins, not normally obvious in lateral or standing/sternal recumbency, are obvious branching structures from venous downstream obstruction. The upshot is that gallbladder wall edema is not pathognomonic for canine AX in the collapsed or weak canine; that veterinarians must resist satisfaction of search error and minimally look past the diaphragm at the FAST DH for pericardial effusion; and the TFAST right PeriCardial View to evaluate contractility before administering large volumes of crystalloids. The author advocates for the performance of Global FAST, the combined use of AFAST and its fluid scoring system, TFAST and Vet BLUE (lung) as part of the physical examination to get a rapid, global free fluid and soft tissue scan of the small animal patient that exceeds the sensitivity (and specificity) of radiography. See Global FAST Proceedings for more detail regarding caudal vena caval characterization.

Figure. The gallbladder halo sign and FAT (distended) CVC in a dog with pericardial effusion (PCE) in A and B. PCE should be ruled out in collapsed, weak dogs suspected of having AX. The single figure on the right showing the FAT (distended) caudal vena cava (CVC) as it traverses the diaphragm (DIA); and the associated distended branching hepatic veins appearing as tree trunks (referred to as the Tree trunk Sign). The character of the CVC is completely different between canines with AX (flat CVC) and canines with pericardial effusion or right-sided heart failure/DCM (FAT CVC). LV: left ventricle; RV: right ventricle; PCE: pericardial effusion; DIA: diaphragm; GB: gallbladder; CVC: caudal vena cava; FF: free abdominal fluid. This material is reproduced with permission of John Wiley & Sons, Inc, Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley ©2014

<table>
<thead>
<tr>
<th>Causes of Gallbladder Wall Edema (the Gallbladder Halo Sign)</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 to the right heart results in hepatic venous congestion</td>
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<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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<td>Pancreatitis</td>
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<tr>
<td>Hypoalbuminemia, 3rd Spacing</td>
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<tr>
<td>Immune-mediated Volume Overload (iatrogenic), from intravenous fluid therapy</td>
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<tr>
<td>Post-Blood Transfusion, unknown pathogenesis, speculate immune-mediated, volume overload</td>
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<tr>
<td>*Causes of Gallbladder Wall Edema (Halo Sign) that Often Present with Acute Collapse or Weakness</td>
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Other potential causes for gallbladder wall edema that are generally present in non-collapsed dogs include 3rd spacing from hypoalbuminemia and vasculitis, primary gallbladder disease including cholecystitis, pancreatitis, and iatrogenic right-sided volume overload. Gallbladder wall edema is often observed in dogs with immune-mediated hemolytic anemia and post-
blood transfusion. Its presence in these subsets does not necessarily indicate canine AX, so it is important to look at the complete clinical profile of these canine patients by doing a good physical exam and performing Global FAST® (AFAST® and its fluid scoring system, TFAST® and Vet BLUE® [lung] as a single examination).

**Canine Anaphylaxis-related, Heparin-induced, Medically-treated Hemoabdomen**

Dogs with anaphylaxis commonly develop abdominal effusion often scored as an abdominal fluid score (AFS) of 1 or 2 using the AFAST®-applied fluid scoring system (see AFAST® and Global FAST® Proceedings); and are most commonly positive at the FAST DH view (makes sense due to acute hepatic venous congestion and hepatic swelling). These low-scoring effusions (AFS 1 and 2) are often self-resolving, the canine patient is non-coagulopathic (PT, aPTT < 25% over upper reference range), and the volume too small for safely performing abdominocentesis. Serial AFAST with AFS, minimally one repeat AFAST 4-hours post-admission, is justified to detect worsening (increasing score [AFS]) or resolution (decreasing score [AFS]) or static (no change in score [AFS]) of the AX-related effusion; and depending on clinical course, a repeat PCV/TS and Coagulation Profile; and AFAST with AFS again repeated after daily patient rounds until the attending veterinarian is certain that AX-related abdominal effusion/presumed low grade hemoabdomen has resolved. Expect that once the patient’s coagulopathy to have resolved, dramatic resolution of AFS to minimal or absent free fluid (AFS 0) within 24-hours. In fact, Global FAST® - AFAST® with AFS, TFAST® and Vet BLUE® - is an even better format over AFAST® alone because Global FAST® provides information on volume status, lung status, and other potential complications occult by physical exam, blood and urine testing, radiography, and vital signs.

Other cases of canine AX have large volume effusions of AFS 3 and 4. Even in these large volume effusions, the coagulation profile may be close to normal and stay close to normal (less than < 25% over upper reference range) on repeat PCV/TS and Coagulation Profile 4-hours post-admission along with AFAST with AFS. These large volume effusions will likewise generally self-resolve within 24-hours if the patient responds favorably to initial resuscitation and therapy for AX including fluid resuscitation +/- epinephrine, histamine-1 receptor blocker (diphenhydramine), histamine-2 receptor blocker (famotidine), and glucocorticoids (dexamethasone sodium phosphate or prednisone). Abdominocentesis should be performed if the free fluid is safely accessible, generally at the most gravity-dependent regions of the abdominal cavity, the AFAST umbilical view (HRU in right lateral recumbency or SRU in left lateral recumbency), when your patient is in lateral recumbency. In our experience, these effusions are hemorrhagic with a comparative abdominal PCV of minimally ≥ 50% of the peripheral PCV. In canine AX cases with abnormal coagulation profiles (greater than > 25% over upper reference range), clotting factors should be replaced as soon as possible, e.g., fresh frozen plasma (FFP). As a crude guideline, 1 in 5-7 canine AX cases require FFP, and 1 in 20 canine AX cases require PRCs. Some of the coagulopathic canines require repeated FFP over several days but more than 1 round of FFP is uncommon if antihistamines and glucocorticoids are used initially to block the second episode of anaphylaxis which leads to persistent continued coagulopathy (WOA Guidelines).

The author treats all canine AX cases with diphenhydramine (H1 receptor blocker) once, famotidine (H2 receptor blocker, mitigates vascular permeability) for several days, and importantly a 5-7 day tapering regimen of anti-inflammatory dosing of prednisone to attenuate the second episode (wave) of AX-related inflammation that propagates and perpetuates coagulopathy. Glucocorticoids must be administered at the time of presentation (initially immediately after fluid resuscitation) and then continued in anti-inflammatory dosages over the next 5-7 days.

In the author’s experience over the past 9-years of recognizing and first describing AX-related heparin-induced hemoabdomen, dogs with AX that are treated with an initial immunosuppressive dose of dexamethasone sodium phosphate (0.3mg/kg) IV then followed by anti-inflammatory prednisone (0.25 mg/kg q 12hrs PO for 3 days then 0.25mg/kg q 24hrs for 3 days) have far less transfusions, much lower cost of care and co-morbidities than those not treated in this manner. The author has seen invoices as high a 10-12K in dogs not treated this way because of the persistent coagulopathy and repeated need for transfusion products over many days. Glucocorticoids have low risk at these dosages, are inexpensive, and very importantly do the following: 1) potently inhibit phospholipase A2 blocking the arachidonic acid pathway mitigating the production of the second episode (wave) of inflammatory products that contribute to bradykinin release and amplification, 2) potently block mast cell degranulation mitigating heparin release, which indirectly limits bradykinin release, and 3) and potently mitigate histamine production. Bradykinin and heparin are likely the most important players in this coagulopathy. Importantly, maropitant and pantoprazole do NOT treat AX.

**Pathophysiology of Canine AX-related Heparin-induced Medically-treated Hemoabdomen**
In theory, the aPTT is more affected by heparin, a natural component of the mast cell granule; thus, PT and aPTT times should be discordant with the aPTT far more prolonged than the PT (opposite of the warfarin or coumadin effect). So when the PT is near normal or mildly elevated with an out of range aPTT, a flag should be raised that the coagulopathy may be a result of AX and heparin release by mast cells. However, the discordance seems unreliable (because of the complexity of the coagulopathy) and the entire clinical patient profile must be considered. The coagulopathy is likely very complex with factors contributing to prolonged clotting times (heparin and tryptase and others) and vascular permeability (bradykinin, products of the Arachidonic Acid Pathway, histamine-2, platelet activating factor, and others) all likely playing roles. In our case series of 11 dogs from nearly 4-years ago, all survived without surgery with complete resolution of their hemorrhagic effusion tracked using Global FAST. Moreover, of the clients that responded to long-term follow-up, AX had not recurred in their dog. The data from this case series is available off our FASTVet Facebook page or may be requested by emailing the author at LearnGlobalFAST@gmail.com or going to our website FASTVet.com

**Conclusion**

It is important to recognize the limitations and additional rule outs for the sonographic finding of a striated gallbladder wall, the so-called gallbladder "halo sign" or "halo effect" or "double rim effect"; and that dogs have a unique AX-related, heparin-induced, medically-treated hemoabdomen complication, and not over-react to stable patients with normal to relatively normal clotting times (less than < 25% over upper reference range) since many will self-resolve with standard AX therapy (fluid resuscitation, low dose epinephrine, HR1-blocker, HR2-blocker (famotidine) continued for several days, and glucocorticoids continued for several days). In other words, many dogs with mildly abnormal coagulation profiles will resolve without transfusion products. Equally important is to know not to take an AX-related coagulopathic canine hemoabdomen to surgery, which could be catastrophic for the dog likely resulting in death. Larger case studies and more sophisticated coagulation assessment are needed to fully understand this perplexing canine AX-related phenomenon; however, author experience has shown that traditional AX therapy is effective in mitigating and correcting AX-related, Heparin-induced, Medically-treated, Canine Hemoabdomen. Lastly, the Global FAST® Approach is a global patient survey that is imperative to avoid “satisfaction of search error” and mistaking a dog with pericardial effusion and right-sided congestive heart failure for canine AX.

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<th>Treatment &amp; Monitoring for Canine Anaphylaxis</th>
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<tr>
<td><strong>First Line</strong></td>
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<tr>
<td>Intravenous Fluids</td>
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<td>Epinephrine</td>
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<td><strong>Second Line</strong></td>
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<tr>
<td><em>Dexamethasone Sodium Phosphate</em> (glucocorticoids)</td>
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<tr>
<td>*Potent Arachidonic Acid Inflammatory Pathway Blocker by inhibiting Phospholipase A2 and Histamine blocker</td>
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<tr>
<td>Diphenhydramine (histamine-1 receptor blocker)</td>
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<td>Famotidine</td>
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Fresh Frozen Plasma

Give if PT, aPTT > 25% over upper reference range and delay as needed.

Follow these cases with frequent PCV q2-4 hours plus Serial AFAST and AFS-scoring until you are confident that the Coagulopathy and Hemoabdomen are Resolving.

Monitoring

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<th>AFAST®</th>
<th>TFAST®</th>
<th>Vet BLUE®</th>
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Global FAST® - combining AFAST® and AFS, TFAST® and Vet BLUE®

AFAST and fluid scoring - on admission and then 4-hours post admission if stable and sooner if unstable.

AFAST and AFS as part of daily patient rounds.

EXPECT resolution of free fluid to small volume AFS 1 and 2 or total resolution within 24-hours when coagulopathy has resolved.

TFAST for volume status and contractility.

Left-heart LA:Ao Ratio on short-axis view fallback non-echo view.

Vet BLUE for left-sided volume overload.

Right-heart RV:LV on long-axis 4-chamber view fallback non-echo view the CVC and hepatic veins.

FAST DH view for right-sided volume overload.

Vet BLUE for lung edema and other respiratory complications.

*Expect lung to be dry in Canine AX unless complications!

References & Further Reading


