

Canine Anaphylaxis: Gallbladder Halo Sign and Medically-Treated Hemoabdomen

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Learning Objectives

- Understand AFAST® and its target organ approach for soft tissue abnormalities and how it relates to the detection of gallbladder wall edema (GBWE)
- Understand how to sonographically recognize GBWE and its anatomy
- Understand other causes of GBWE other than canine anaphylaxis (AX) in the acute setting
- Understand the principles of diagnosing canine AX
- Understand this newly described (first by the author) subset of canine hemoabdomen that is medically-treated

Introduction

The lecture will not cover details regarding the pathophysiology of anaphylaxis of which there exist many excellent published descriptions. Rather, the author 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. Moreover, gallbladder wall edema is *not* pathognomonic for canine anaphylaxis, and important rule outs that can confound the diagnosis to the detriment of the patient care will be discussed. Lastly, a newly described, fascinating, medically-treated hemoabdomen complication, referred to as a "canine anaphylactic-related, heparin-induced hemoabdomen" by the author will be discussed (Lisciandro JVECC 2016; Hnatusko et al. 2019; Caldwell et al. 2019). The major reason for this lecture is that many veterinarians are now using ultrasound, specifically FAST exams, as a lifesaving first-line screening test. As a result, free fluid and other soft tissue changes are being detected that would otherwise be missed *without* ultrasound. This lecture disregards the obvious canine having a mild hypersensitivity reaction with the classic cutaneous signs of angioedema, pruritus and urticaria, but rather focuses on the *single* often unwitnessed *Hymenoptera* envenomation causing anaphylaxis in a previously healthy, acutely collapsed dog, most commonly having *no* cutaneous signs. 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 hemorrhage, and non-specific histopathology.

The AFAST-TFAST® 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 bile-filled lumen that is homogeneously anechoic (black). The gallbladder wall is characterized sonographically as a thin hyperechoic (white) line in both canines and felines despite normal thickness reported to be < 2-3 mm. Conversely, the sonographic features of the canine and feline gallbladder when intramural edema is present are characterized as sonographic striation of hyperechoic-anechoic-hyperechoic (white-black-white) or hyperechoic-hypoechoic-hyperechoic (white-gray-white) and is generally easy to recognize by the non-radiologist sonographer at the AFAST®-TFAST® Diaphragmatico-Hepatic (DH) View. So, where does this gallbladder wall edema concept originate? In a 2009 study,

Quantz et al. published a brilliant study that correlated the presence of a thickened, edematous, sonographically-striated gallbladder wall, referred to as the gallbladder "halo effect" or "double rim effect" or "halo sign" with canine anaphylaxis (AX). Their study design was a result of recognizing that in a canine AX research model, intramural gallbladder wall edema was commonly present. Their oversight in hindsight, was, by performing only a "focused" or "targeted" gallbladder exam without an AFAST® and an AFAST® -assigned abdominal fluid score (better a Global FAST® approach), they missed potential rule-outs and the canine anaphylactic hemoabdomen first described by the author (Lisciandro 2016; Lisciandro 2014).

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

Anaphylactic (AX)-related gallbladder edema is specific to canines because the canine shock organ, where the highest concentration of mast cells is located, is their liver and gastrointestinal tract. In contrast, the shock organ of cats and people are 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 within the portal circulation, causing hepatic venous sphincter constriction and massive hepatic venous congestion (Quantz et al. 2009). 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 those associated with hepatic venous congestion from right-sided congestive heart failure (Lisciandro 2019). Other rule outs are listed in the Chart. 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, whereas the liver enzyme serum alanine transaminase (ALT) may lag several hours; and that cutaneous signs are often *absent* in ~40% of canine AX cases. However, in our experience, cutaneous signs are absent in nearly 95% of cases.

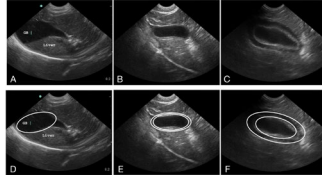


Figure. Gallbladder Wall in Normalcy and in Canine Anaphylaxis. Normal expected sonographic appearance of the gallbladder wall in canines as a thin white (hyperechoic) line juxtaposed with various degrees of sonographic gallbladder wall striation. The sonographic striation presents the outer and inner walls as a white lines with the edema (black or gray) in between, representing different degrees of intramural gallbladder edema in dogs with anaphylaxis. *This material is reproduced with permission of John Wiley & Sons, Inc., Point-of-Care Ultrasound Techniques for the Small Animal Practitioner, 2nd Edition, Wiley ©2021 and Greg Lisciandro, Hill Country Veterinary Specialists, FASTVet.com ©2014, 2021.*

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

The Quantz et al. study documented that serum ALT as a marker for canine AX was not as immediate as the ultrasound finding of gallbladder wall edema. The serum ALT may not spike in value for up to 2-4 hours post-insult, whereas gallbladder wall edema occurs within minutes. Their study documented a mean value for ALT of ~ 400 IU/L in anaphylactic dogs.

The Classic Constellations of Signs for Canine Anaphylaxis

Keeping in mind the canine shock organ being the liver and gastrointestinal tract, traditional means of diagnosing canine AX have relied on a history of acute collapse in a previously healthy dog often

accompanied by gastrointestinal signs such as vomiting and defecation. Hemoconcentration (packed cell volume > 52%) often occurs, due to massive fluid shifts of up to 35% of the intravascular volume to the interstitial compartment within minutes, caused by massive histamine release into the portal circulation. This histamine release results in hepatic venous sphincter constriction and massive hepatic venous congestion and gallbladder wall edema, recognized sonographically. The massive hepatic venous congestion, along with other factors that contribute to the acquired coagulopathy (heparin, histamine-2, bradykinin, tryptase, platelet activating factor, prostacyclins and others), lead to hepatic oozing of blood into the abdominal cavity creating various degrees of hemoabdomen. ALT is also elevated with a median of ~ 400 IU/L in anaphylactic dogs. Importantly, the weather should also be considered because in San Antonio, Texas, canine AX most often occurs during the autumn and spring, when there are warm days followed by cool nights, making *Hymenoptera* species lethargic and less likely to move away from the unsuspecting dog walking and sniffing outdoors in the yard.

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) (Lisciandro 2014, 2019). 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 rapidly and habitually addressed by always looking cranial to the diaphragm at the FAST DH view for the classic "Racetrack Sign" of pericardial effusion. The "Racetrack Sign" refers to the rounding of pericardial effusion around the muscular apex of the heart (Lisciandro 2014, 2016). In the absence of pericardial effusion and with the presence of a distended CVC with hepatic venous distension, the TFAST® echo views rapidly screen for other right-sided problems including increased RV:LV ratio (pulmonary hypertension) and poor systolic dysfunction (dilated cardiomyopathy).

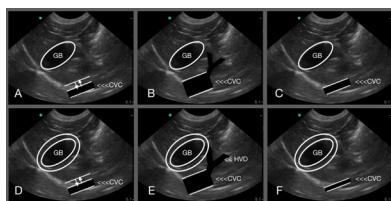


Figure. Integrating Gallbladder Wall Edema with Caudal Vena Cava and Hepatic Venous

Characterization. The integration of caudal vena cava and hepatic venous characterization is helpful because in cases of canine anaphylaxis, the CVC will be small (flat) because of the life-threatening hypovolemic/distributive shock. In contrast, right-sided congestive heart failure cases will have a CVC that will be distended (FAT) often with hepatic venous branching (Tree Trunk Sign), most commonly caused by pericardial effusion. By integrating gallbladder wall edema findings with characterization of the CVC and hepatic veins the probability increases for a correct assessment. GB: gallbladder; CVC, caudal vena cava; HVD, hepatic venous distension. *This material is reproduced with permission of John Wiley & Sons, Inc., Point-of-Care Ultrasound Techniques for the Small Animal Practitioner, 2nd Edition, Wiley ©2021 and Greg Lisciandro, Hill Country Veterinary Specialists, FASTVet.com ©2014, 2021.*

Moreover, the 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 an indirect marker for volume status and central venous pressure (CVP). The integration of CVC characterization prevents "satisfaction of search error"

because in AX the CVC is flat or small (no volume, low CVP) with minimal variation (< 10%) in its maximum height. In contrast, the CVC characterization in pericardial effusion and right-sided cardiac cases is diametrically different being FAT or distended (backflow of blood, high CVP) with minimal variation (< 10%) in its maximum height. When the CVC is FAT from a high CVP, hepatic veins, not normally apparent in lateral or standing/sternal recumbency, become obvious branching structures from venous downstream obstruction, referred to as the "Tree Trunk Sign" (Lisciandro 2014, 2016). The upshot is that gallbladder wall edema integrated with TFAST® information increases the probability of correctly assessing the patient. Moreover, the Global FAST® approach is even more effective for acquiring a standardized set of imaging data points and thus avoiding "selective imaging" that leads to confirmation bias error; and "satisfaction of search error" that leads to stopping the exam once an abnormality is found. These errors are problematic with "focused" and "targeted" and now referred to as POCUS (point-of-care ultrasound exams). See *Global FAST® Proceedings for more detail regarding volume status and caudal vena caval characterization.*

Table. Rule Outs for the Finding of Gallbladder Wall Edema in Dogs and Cats

Condition	Expected Characterization of the Caudal Vena Cava (CVC)	Speculated Pathophysiology
*Canine Anaphylaxis	flat, hypovolemic CVC	Massive histamine release resulting in acute marked hepatic venous congestion
*Pericardial Effusion	FAT, distended, hypervolemic CVC	Marked hepatic venous congestion from obstruction of blood flow to the right atrium
*Right-sided Congestive Heart Failure (dilated cardiomyopathy, pulmonary hypertension, tricuspid disease)	FAT, distended, hypervolemic CVC	Marked hepatic venous congestion from backflow of blood from the right atrium
Cholecystitis	variable	Direct inflammation
Pancreatitis	variable	Direct inflammation
Hypoproteinemia (3rd spacing)	variable	Vascular leak
Immune-mediated Hemolytic Anemia	variable	Likely immune-mediated and volume overload
Post-transfusion	variable to FAT, hypervolemia	Likely immune-mediated and volume overload
<i>* Conditions that are most important to consider in the acute triage setting of acute collapse and weakness in a previously absolutely healthy patient (dog). With Permission Dr. Gregory Lisciandro, Hill Country Veterinary Specialists, FASTVet.com, Spicewood, Texas, ©2018, 2019.</i>		

Other more common 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 of patients *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®.

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 (modified AFS < 3, see AFAST[®] Proceedings) using the AFAST[®]-applied fluid scoring system (see AFAST[®] and Global FAST[®] Proceedings); and are most commonly positive at the FAST DH View, which 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 the upper reference range), and the volume of ascites too small for safely performing abdominocentesis. Serial AFAST[®] with AFS, minimally at least one repeat AFAST[®] 4-hours post-admission (sooner if questionable or unstable status), and then during patient rounds and rechecks, is justified to detect worsening (increasing score [AFS]) or resolution (decreasing score [AFS]) of the AX-related presumed hemorrhagic effusion. A repeat packed cell volume/total solid (PCV/TS) and coagulation profile should be performed 4-hours post-admission in dogs with increasing scores, and then dependent on clinical course and AFAST[®] with AFS findings. The attending veterinarian should continue performing AFAST[®] with AFS until they are certain that the acquired coagulopathy has been corrected and the AX-related abdominal effusion, presumed low grade hemoabdomen has resolved. In fact, Global FAST[®] - AFAST[®] with AFS, TFAST[®] and Vet BLUE[®] - is an even better format over AFAST[®] and AFS 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 will have large volume effusions of AFS 3 and 4. Even in these large volume effusions, the coagulation profile *may still be close to normal and stay close to normal* (< 25% above upper reference range). 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 when the free fluid is safely accessible and is generally performed at the most gravity-dependent regions of the abdominal cavity, the AFAST[®] hepato-renal umbilical view. In our experience, these effusions are hemorrhagic with a comparative abdominal PCV of ≥ 50% of the peripheral PCV. In canine AX cases with abnormal coagulation profiles (> 25% over upper reference range), clotting factors should be replaced as soon as possible, i.e. fresh frozen plasma (FFP). As a crude guideline from the author's experience, 1 in 5-7 canine AX cases require FFP, and 1 in 15 canine AX cases require a second round of FFP, and rarely do dogs require blood transfusions when treating with histamine-2 receptor antagonists and glucocorticoids at the time of diagnosis and not waiting for complications to worsen. The glucocorticoids importantly mitigate the "second episode or anaphylaxis" that contributes to the windup phenomenon creating a persistent coagulopathy.

Treatment Guidelines

The author treats all canine AX cases with diphenhydramine (H1 receptor blocker) once, H2-receptor antagonists (famotidine) over several days because they mitigate vascular permeability, and most importantly a tapering regimen of anti-inflammatory dosing of dexamethasone sodium phosphate or prednisone to mitigate the "second episode" of AX-related inflammation. This "second episode" of anaphylaxis *propagates and perpetuates* this unique acquired coagulopathy of dogs. Glucocorticoids must be administered at the time of presentation and are then continued at anti-inflammatory dosages in AFAST[®] fluid positive cases. In the author's experience, over the past 9 years of recognizing and first describing AX-related heparin-induced hemoabdomen in the veterinary literature, dogs with AX that are treated with an initial immunosuppressive dose of dexamethasone sodium phosphate (0.3mg/kg) IV then followed by anti-inflammatory amounts of prednisone (0.25 mg/kg q 12hrs PO for 3 days then 0.25mg/kg q 24hrs for 3 days) have far less transfusions and much lower cost of care and co-morbidities

than those not treated in this manner. The author has seen invoices as high as \$10,000-12,000 USD in dogs not treated in this manner because of the persistent acquired coagulopathy and the repeated need for transfusion products along with several days of hospitalized care.

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 and mitigating the production of the "second episode" of AX and its inflammatory products that contribute to heparin and bradykinin release and coagulopathy amplification, 2) *potently* block mast cell degranulation mitigating heparin release, which indirectly limits bradykinin release, and 3) *potently* mitigate histamine release. *Of note, maropitant and pantoprazole do not treat the "second episode" of AX. The author's treatment chart is available at FASTVet.com under Membership and "Free Resources."*

Pathophysiology of Canine AX-related Heparin-induced Medically-treated Hemoabdomen

In theory, the aPPT 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. This phenomenon is opposite of the expected discordance with warfarin or coumadin. So, when the PT is near normal or mildly elevated with a discordant often 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, likely because of the complexity of the acquired coagulopathy, and the entire clinical patient profile must be considered. The coagulopathy is likely very complex with many factors contributing (heparin) and vascular permeability (bradykinin, products of the arachidonic acid pathway (prostacyclins), histamine-2, platelet activating factor, tryptase, and others). In our case series of 11 dogs from nearly 4 years ago, all survived (follow-up > 3-years) *without* surgery with complete resolution of their hemorrhagic effusion (tracked using Global FAST[®]). Moreover, AX had *not* recurred in any of this small number of dogs.

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", and that dogs have a unique AX-related, heparin-induced, medically-treated hemoabdomen complication. When recognized, it is important for the clinician to not over-react to stable resuscitated patients with normal to relatively normal clotting times (< 25% over upper reference range) since many will *self-resolve within 24-hours* with AX therapy guidelines provided by the author. In other words, many dogs with mildly abnormal coagulation profiles will resolve *without* transfusion products. However, the use of glucocorticoids and histamine-2 antagonists are imperative in AFAST[®] fluid positive cases with presumed hemoabdomen in low scoring dogs (AFS <3) or in confirmed hemoabdomen in the higher scoring dogs via abdominocentesis and fluid analysis. Equally important is to know not to take an AX-related, heparin-induced, coagulopathic canine hemoabdomen to surgery, which could be catastrophic for the canine patient, 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, and death is rare. Lastly, the Global FAST[®] approach is imperative to avoid "satisfaction of search error" and "selective imaging" and "confirmation bias error."

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