Gallbladder Mucocoele: A Short Review

Philip R Judge BVSc MVS PG Cert Vet Stud MACVSc (Vet. Emergency and Critical Care; Medicine of Dogs)

Definition and Pathogenesis

Canine gallbladder mucocoele (GBM) is a condition resulting in distension of the gallbladder, secondary to progressive, inappropriate accumulation thick, gelatinous bile, produced by the gallbladder epithelium.

In some cases, bile accumulation may extend into the cystic, hepatic, and common bile ducts, resulting in variable degrees of bile duct obstruction.

Progressive expansion of a GBM can also lead to gallbladder wall ischemia and necrosis, and eventual gallbladder rupture, with bile peritonitis ensuing.

The clinical importance of GBM is thought to be primarily related to risks of gallbladder rupture, infection, extrahepatic biliary duct obstruction, and systemic inflammatory response syndrome that can occur secondary to gallbladder necrosis or infarction.

Aetiology

The cause of GBM is likely multifactorial and remains uncertain in many dogs. What is known is that there is abnormal gallbladder mucous production

Suspected risk factors for development of GBM that are frequently mentioned, but have been disproven either based on clinical or experimental evidence include

1. Disordered gallbladder motility
2. Gallbladder obstruction
3. Biliary infection
4. Genetic defect in ATP Binding Cassette Subfamily B Member 4 (ABCB4)

Gallbladder mucocoele formation is typically diagnosed in older-aged (median, 10 years) pure breeds of dog such as the Shetland sheepdog, Cocker spaniel, Miniature Schnauzer, Pomeranian, Chihuahua, and others. Two cases have been reported in cats.

Affected dogs have a high incidence of concurrent endocrinopathy (hyperadrenocorticism or hypothyroidism), and a variable concurrence of hypercholesterolaemia or hypertryglyceridaemia.

In one study, dogs treated with imidacloprid were 2.3 times more likely to have GBM as untreated control dogs; with Shetland Sheepdogs 9.3 times more likely to have GBM than untreated Shetland Sheepdogs, suggesting a possible association

The presence of strong breed predisposition, and concurrent endocrinopathy or hyperlipidaemia suggest a significant influence of both genetic and metabolic factors on disease pathogenesis. A study looking at bile composition in heathy dogs, versus dogs with GBM revealed a 33-fold decrease in serum adenosine 5'-monophosphate (AMP), lower quantities of precursors required for synthesis of energy transporting nucleotides, and increases in citric acid cycle intermediates, suggest excess metabolic energy and a carbon surplus. Altered quantities of compounds involved in protein translation and RNA turnover, together with accumulation of gamma-glutamylated and N-acetylated amino acids in serum suggest abnormal regulation of protein and amino acid metabolism. Increases in lathosterol and 7α-hydroxycholesterol suggest a primary increase in cholesterol synthesis and diversion to bile acid formation. There was also a significant decrease in quantity of biologically active compounds that stimulate biliary ductal fluid secretion including adenosine,

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cAMP, taurolithocholic acid, and taurocholic acid, suggesting significant metabolic disruption in dogs with mucocoele formation.

Studies of normal and affected gallbladders identified that mucocoele formation is associated with excess secretion of Muc5ac, a gel-forming mucin, by the gallbladder epithelium. Muc5sac is highly cross-linked and entangled by mucin-interacting proteins. During exocytosis, mucus granules fail to unpack their contents or break free from the vesicles and remain tethered to one another and to the gallbladder epithelium.

Clinical Findings and Diagnosis:

Clinical signs associated with gallbladder mucocoele are often nonspecific and vague. In some cases, no clinical signs are present, and a mucocoele is discovered incidentally on abdominal ultrasound.

Common clinical findings include:

- decreased appetite
- anorexia
- lethargy
- vomiting
- diarrhoea

Patients progressing to gallbladder rupture may show additional clinical symptoms, including:

- abdominal pain or splinting
- abdominal discomfort on palpation
- jaundice
- tachypnoea
- tachycardia
- pyrexia
- abdominal distension
- polyuria/polydypsia

Clinical pathology evaluation typically reveals

- leukocytosis, with neutrophilia +/- left shift
- elevated liver enzymes
- hyperbilirubinaemia
- hypercholesterolaemia (may or may not be present)

Culture of the gallbladder wall may reveal colonisation with the following bacteria:

- *Escherichia coli*
- *Enterobacter* spp
- *Enterococcus* spp
- *Staphylococcus* spp
- *Micrococcus* spp
- *Streptococcus* spp.

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Ultrasonography may detect the following:

- Mucocoele is characterized by the appearance of the stellate or finely striated bile patterns and differ from biliary sludge by the absence of gravity dependent bile movement.
- Gallbladder wall thickness and wall appearance were variable and nonspecific.
- The cystic or common bile duct can be normal sized, even in dogs with biliary obstruction
- Loss of gallbladder wall integrity and/or gallbladder rupture may be present, especially about the fundus
- Pericholecystic hyperechoic fat or fluid is suggestive of but not diagnostic for a gallbladder rupture.
- Hepatomegaly with either a heterogeneous or hyperechoic hepatic parenchyma may be present.
- Ultrasonography has a low sensitivity (as low as 56.1%) for detection of gallbladder rupture
- In one study, 20% of dogs with gallbladder mucocoele diagnosed at surgery, had no evidence of GBM on ultrasound evaluation

A grading system for gallbladder mucocoeles has been developed:

GBM Type	Description
1	**Immobile echogenic bile**
2	**Incomplete stellate pattern**
3	**Typical stellate pattern**
4	**Kiwi-like pattern and stellate combination**
5	**Kiwi-like pattern with residual central echogenic bile**
6	**Kiwi-like pattern**
Rupture	**Concern for GB rupture**

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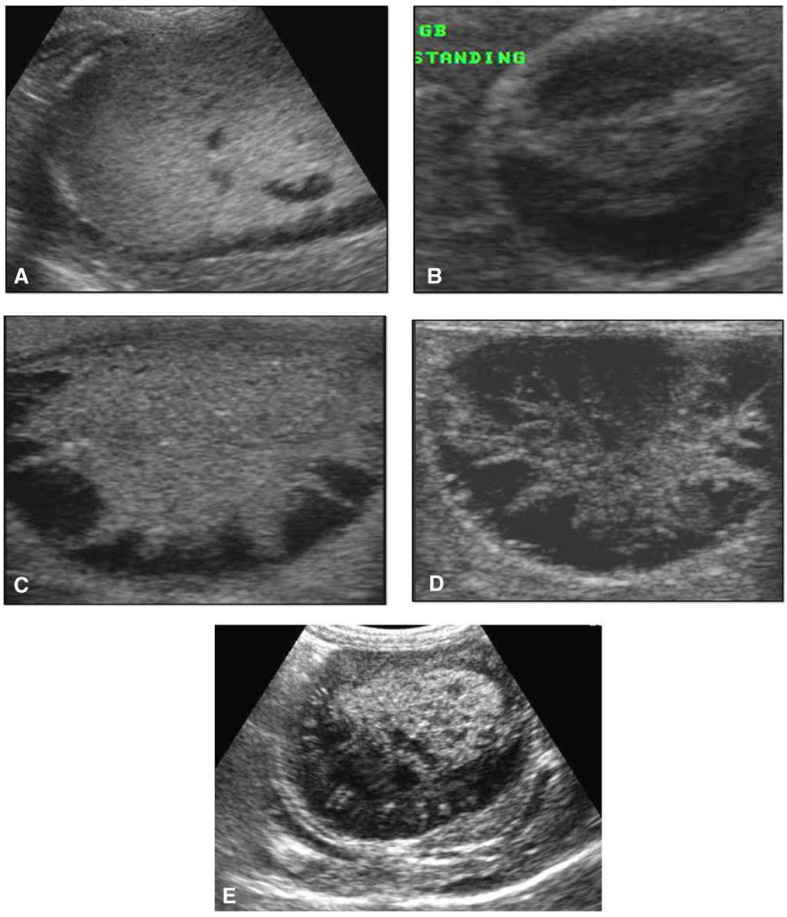

Ultrasound images illustrating five patterns of gallbladder mucocele identified in dogs included in the current study. (A) Type 1 was defined as echogenic immobile bile occupying the gallbladder. (B) Type 2 was defined as an incomplete stellate pattern. Note a few hypoechoic bile casts along the gallbladder wall with central echogenic sludge. (C) Type 3 was defined as a typical stellate pattern. Note of the many definite hypoechoic bile casts along the gallbladder wall with central echogenic bile sludge. (D) Type 4 was the kiwi fruit like pattern and stellate combination. Note hypoechoic bile casts accompanying more fine striations with a central echoic region. (E) Type 5 was the kiwi fruit like pattern with residual central echogenic bile.

Image and legend from: Choi J, Kim A, Keh S, Oh J, Kim H, Yoon J. Comparison between ultrasonographic and clinical findings in 43 dogs with gallbladder mucoceles. Veterinary Radiology & Ultrasound. 2014 Mar;55(2):202-7.

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Treatment:

1. Dogs without signs of mucocoele leakage or biliary tree obstruction at the time of initial diagnosis have traditionally been managed with medical treatment. ***However, it should be stressed that resolution of GBM with medical treatment is very rare, and the "wait and see" approach, before surgical intervention when symptoms or disease severity progress, being associated with an increased likelihood of gallbladder rupture and poor prognosis.***
2. Medical therapy is as follows:
    a. Choleretic medication: ursodeoxycholic acid (15–25 mg/kg, PO divided q 12 hrs and given with food)
    b. Hepatic anti-oxidants: SAMe (20–40 mg/kg/day, PO, after an overnight fast
    c. Antimicrobial coverage: amoxycillin 20 mg/kg PO q 12 hrs.
    d. Biochemical and ultrasonographic evaluations every 6 weeks are useful to monitor treatment response or syndrome progression

    Gallbladder mucocoele rarely resolve with medical treatment. Progression in any clinical, clinicopathologic, or imaging parameter indicates poor control and need for urgent surgical intervention.

3. Surgical Treatment: Cholecystectomy is the treatment of choice for GBM, regardless of clinical signs. Urgent surgical treatment is recommended in patients with clinical signs and clinicopathologic findings consistent with biliary tree inflammation, obstruction, or rupture.
    Complications from cholecystectomy include
    a. Bile leakage due to failure of cystic duct ligatures (3%–8%)
    b. Haemorrhage secondary to failure of cystic artery ligations or from damage to the liver parenchyma during gallbladder dissection
    c. Failure to document bile duct patency prior to cholecystectomy
4. Post-Surgical Treatment
    a. Antibiotic therapy: Infection may be present in the biliary tract of up to 32% of patients with GBM. Broad-spectrum antimicrobials are recommended before surgical intervention, and may be considered for several days following cholecystectomy to reduce incidence of post-operative cholangitis
    b. Chronic choleretic therapy: is recommended, especially for Shetland Sheepdogs in which a genetic risk is suspected, leading to creation of biliary sludge.
    c. Manage underlying diseases
        i. Causes of hyperlipidaemia or endocrine disorders should be identified and managed appropriately.
        ii. Cholangiohepatitis complicated by infection will require antibiotic therapy
    d. Analgesia: routine post-operative analgesia should be provided with opioid and adjunctive therapy (ketamine, lidocaine etc.) as indicated.

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Prognosis:

Risk factors for poor outcome in GBM include

a. renal azotemia
b. the presence of septic bile peritonitis
c. dyspnoea
d. leukocytosis
e. prolongation of partial thromboplastin time
f. hypotension – particularly in the immediate post-operative period
g. elevations in post-operative blood lactate concentrations
h. sepsis
i. DIC

In dogs, mortality rates with GBM carry a 20-40% mortality rate; and in cats, a 40-60% mortality rate However, cases in which an early diagnosis is made, and surgical intervention is performed may have a much better prognosis. This is supported by a recent study, which found significantly lower mortality (2%) in dogs undergoing elective cholecystectomy compared to those undergoing emergency cholecystectomy (22%-40%).

Additionally, a long-term study looking at survival of dogs with GBM showed surgical treatment of GBM results in a significantly longer MST after initial diagnosis compared to dogs treated with medical management alone or with medical management followed by surgical treatment.

In the same study, increasing severity of GBM type diagnosed with ultrasound was significantly associated with decreased survival, suggesting that ultrasound images may allow better prognostication beginning treatment. This finding also suggests that early detection of low-scoring GBM may allow for earlier intervention and improved outcomes.

Importantly, if an underlying endocrinopathy is detected and managed, it is possible for GBM to resolve with medical management

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