JOURNAL OF
Veterinary Emergency
AND Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care **26**(4) 2016, pp 559–567
doi: 10.1111/vec.12482

Retrospective evaluation of acute liver failure in dogs (1995–2012): 49 cases

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Abstract

Objective – To characterize the clinical presentation and outcome of dogs with acute liver failure (ALF).
Design – Retrospective case series from January 1995 to December 2012.
Setting – University teaching hospital.
Animals – Forty-nine dogs were diagnosed with ALF defined as the acute onset of clinical signs accompanied by serum hyperbilirubinemia and coagulopathy (prothrombin time >1.5 times the upper limit of the reference interval) with or without signs of hepatic encephalopathy.
Methods – Medical records were retrospectively analyzed for clinical presentation, history, physical examination findings, clinicopathologic data, diagnostic imaging findings, hepatic histopathology, treatment, and outcome.
Main Results – Presenting signs included anorexia (28/49, 57%), vomiting (25/49, 51%), neurologic abnormalities (17/49, 35%), and polydipsia/polyuria (10/49, 20%). Neurologic impairment compatible with hepatic encephalopathy occurred at some point during hospitalization in 28/49 (57%) of dogs. Common clinicopathologic abnormalities on presentation other than hyperbilirubinemia and increased serum liver enzyme activity included thrombocytopenia (25/49, 51%), hypoalbuminemia (23/49, 46%), leukocytosis (17/49, 34%), anemia (14/49, 29%), hypokalemia (13/49, 27%), and hypoglycemia (10/49, 20%). The causes of ALF included neoplasia (13/49, 27%), presumptive leptosporosis (4/49, 8%), and ischemia (1/49, 2%). The remaining cases were idiopathic although 15 of these dogs had exposure to possible hepatotoxins. Common lesions in the 35/49 (71%) dogs that had hepatic histopathology were necrosis (19/39, 48%), lipidosis (16/39, 41%), vacuolar change (7/49, 14%), and inflammation (4/49, 8%). Complications included ascites (20/49, 41%), bleeding tendencies (14/49, 29%), pancreatitis (12/49, 24%), and acute tubular necrosis (11/49, 22%). Seven (14%) dogs survived to discharge. Survivors had higher alanine aminotransferase activity, and were more likely to maintain normal albumin concentrations and not develop clinical bleeding or ascites during hospitalization.
Conclusions – Canine ALF is associated with multiple etiologies and a high mortality rate. Strategies to increase survival are urgently required.

(J Vet Emerg Crit Care 2016; 26(4): 559–567) doi: 10.1111/vec.12482

Keywords: canine, coagulopathy, encephalopathy, hepatopathy

Abbreviations

ALF	acute liver failure
ALT	alanine aminotransferase
FFP	fresh frozen plasma
HE	hepatic encephalopathy
PT	prothrombin time
aPTT	activated partial thromboplastin time

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Authors declare no conflict of interests.

Presented in part at the ACVIM Forum 2011, Denver, Colorado.

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Submitted December 03, 2014; Accepted May 31, 2015.

Introduction

Acute liver failure (ALF) is a clinical syndrome defined in people as the acute onset of severe hepatic insufficiency as manifested by increases in serum transaminase activity and bilirubin concentration, accompanied by coagulopathy and signs of encephalopathy.[1–3] Underlying causes for ALF in people include viral infection, drug-induced, toxins, metabolic disorders, neoplasia, and auto-immune hepatitis; however, approximately 20% of human ALF remains of indeterminate etiology.[2] The overall survival for ALF in people without liver transplantation is approximately 15%.[2]

In the veterinary literature, isolated case series of dogs with acute hepatic disease related to toxins, drugs, neoplasia, or infection have been reported.[4–22] Although these reports include dogs that fit the criteria for ALF, no comprehensive study reporting solely on dogs with ALF exists. A single study of dogs with acute hepatitis has been reported, but based on clinical findings, this population of dogs did not fit the criteria for ALF.[23] The objective of this study is to describe the clinical presentation, laboratory values, histopathological findings, etiology, secondary complications, and outcome associated with ALF in dogs.

Materials and Methods

Medical records were reviewed retrospectively for cases of canine ALF from January 1995 to December 2012. ALF was defined as the development of acute clinical signs with concurrent identification of hyperbilirubinemia and coagulopathy (ie, prolongation of prothrombin time (PT) greater than 1.5 times the upper limit of the reference interval).[1–3] This definition was derived from human medicine, as no clear definition of ALF in dogs exists.[1–3] Considering the difficulty in retrospectively assigning the presence of diffuse cerebral signs suggestive of hepatic encephalopathy (HE), we did not include encephalopathy in our definition of ALF. In children, HE is often omitted from the diagnosis due to difficulty recognizing this syndrome in early stages.[1–3] Data collected included signalment, clinical signs, history including drug or toxin exposure, physical examination findings, routine clinicopathologic tests, including CBC, serum biochemical profile, urinalysis, coagulation profiles, hepatic cytology or histopathological evaluation, treatments, and outcome. A single pathologist (R.M.P.) retrospectively reviewed all the hepatic biopsies according to published guidelines.[24] Blood samples for biochemical evaluation collected at presentation (initial data) and when possible, again at the time of discharge or euthanasia (final data), were evaluated.

A cause for ALF was determined whenever possible from historical accounts of ingestion of a known hepatotoxin, serology for infectious disease, and from the results of hepatic histopathology or fine-needle aspirate evaluation. Concurrent preexisting diseases and secondary complications were noted. Dogs were classified as survivors if they were discharged from the hospital.

Statistical Evaluation

Box and whisker plots as well as tests for skewness and kurtosis were conducted to evaluate data distribution. Since most of the data were non-Gaussian, nonparametric tests were used for comparison and data expressed as median with range. Data were then compared between survivors and nonsurvivors using the Mann–Whitney *U*-test. Statistical significance was set at $P \leq 0.05$ (2-tailed) and adjusted for multiple tests. Two by two contingency tables were constructed to analyze categorical data between survivors and nonsurvivors and compared using a 2-tailed Fisher's exact test with P less than or equal to 0.05 considered significant. Normal data were expressed as mean $\pm$ SD.

Results

Signalment and clinical signs

Forty-nine cases were identified representing 26 breeds including 7 Labrador Retrievers, 5 Golden Retrievers, and 3 mixed breed dogs. Median weight was 24.5 kg (range 1.36–66.8 kg). Twenty dogs (41%) were neutered males, 20 (41%) were neutered females, 8 (16%) were intact males, and 1 (2%) dog was an intact female. Age ranged from 1 month to 13 years (mean, 5.6 $\pm$ 3.7 y). Presenting clinical signs were variable however the most common signs included anorexia (28/49, 57%), vomiting (25/49, 51%), polydipsia (10/49, 20%), and neurologic signs consistent with HE such as dull mentation, circling, head pressing, or seizures (17/49, 35%).

Seven dogs died and 35 dogs were euthanized due to clinical deterioration or the escalating costs of treating a critically ill animal. Seven dogs (14%) survived to discharge. The median hospitalization time for all dogs was 3 days (range 1–12 d). The median hospitalization times for survivors and nonsurvivors were 6 days (range 5–12 d) and 2 days (range 1–8 d), respectively.

Causes of ALF

Overall, 32/49 (65%) dogs had evaluation of hepatic tissue by aspirate, biopsy, or necropsy. Twenty-three of these 32 dogs (71%) were necropsied, 11/49 (22%) had ante-mortem liver biopsies, and 6/49 (12%) had a fine-needle aspirate of the liver. Eight (16%) of the aforementioned dogs underwent a combination of methods to obtain hepatic tissue. A summary of pathological findings is in Table 1. The most common hepatic lesions were necrosis (47%) which was diffuse, centrolobular, or multifocal in 7/15 (47%), 3/15 (20%), and 5/15 (33%) cases, respectively. Hepatic degenerative changes included lipidosis (40%) and vacuolar change (19%). Neoplasia was identified in 13/32 (40%) of the cases. Acute hepatitis characterized by pyogranulomatous or lymphoplasmacytic inflammation was present in 21% of dogs. Four dogs (8%) had some degree of biliary proliferation and 1 (2%) dog each had bile duct necrosis or gallbladder inflammation. Lymphoma was diagnosed

Table 1: Biopsy and necropsy findings in dogs with acute liver failure

Organ	Pathologic finding	Number affected	Organ	Pathologic finding	Number affected
Liver	Necrosis	15/32	Kidney	Acute tubular necrosis	11/23
	Lipidosis	13/32		Chronic glomerulonephritis	4/23
	Inflammation	7/32		Interstitial nephritis	2/23
	Vacuolar degeneration	6/32	Thrombosis	Portal vein thrombosis	1/23
	Neoplasia	13/32		Splenic vein thrombosis	1/23
Biliary tree	Biliary proliferation	4/32		Pulmonary thromboembolism	2/23
	Bile duct necrosis	1/32		Hepatic artery	2/23
	Cholecystitis	1/32	Hemorrhage	Melena	14/23
Pancreas	Inflammation	5/23		Petechiation	5/23
	Necrosis	3/23		Ecchymosis	5/23
	Atrophy	1/23		Cerebral	2/23
Gastrointestinal	Inflammation	7/23		Hemoabdomen	2/23
	Ulceration	4/23			
	Necrosis	1/23			

in 2 (4%) dogs by aspirates of grossly normal popliteal lymph nodes.

In animals with a full necropsy ($n = 23$), histopathological abnormalities were frequently present in other organs (Table 1). Concurrent renal lesions were identified in 18/23 (78%) dogs and consisted of acute tubular necrosis in 11 dogs, chronic membranous glomerulonephritis in 4 dogs, and interstitial nephritis in 3 dogs. Concurrent pancreatic and gastrointestinal lesions were present in 9/23 (39%) dogs. Five dogs had pancreatitis, 3 with concurrent necrosis, and 1 with atrophy. Gastrointestinal findings were characterized by ulceration in the stomach (2), duodenum (1) and colon (1), neutrophilic or lymphocytic small intestinal inflammation (7), or jejunal necrosis (1). Pleural effusion was present in 9 dogs and peritoneal effusion in 14. Four dogs had gross evidence of thrombosis at necropsy, 2 with pulmonary thromboembolism, and 2 with hepatic infarcts. One of the dogs with a hepatic infarct also had a splenic and portal vein thrombosis.

An etiology was determined from history, serology, or hepatic histopathology in 18 cases. The most commonly identified cause was neoplasia (13 dogs). This included 8 dogs with hepatic lymphoma, 2 with poorly differentiated round cell tumors, and 1 each with a mast cell tumor, an epithelial carcinoma, and a metastatic carcinoma. Four dogs had suspected leptospirosis based on positive acute titers. One dog had an ischemic cause with a thrombus in a large hepatic artery and multiple thrombi in the large hepatic veins on necropsy. Of the other 31 (63%) cases in which no cause was identified, 15 dogs had exposure to potentially hepatotoxic substances including nonsteroidal anti-inflammatory agents (7), phenobarbital (3), trimethoprim sulfa (1), glucosamine manufactured for equine use (1), doxycycline (1), cephalexin (1), and mushrooms (1). In the remainder of the dogs (16), no underlying cause was identified. Of the 7 dogs that survived, an underlying etiology was available for 2 dogs (suspected carprofen toxicity and leptospirosis).

Laboratory findings

Initial laboratory findings in survivors and nonsurvivors are summarized in Table 2. Findings on CBC included thrombocytopenia (26/49 dogs [53%]; median 146 $\times$ 10^9/L with range 9–653 $\times$ 10^9/L), leukocytosis 17/49 [34%], and leukopenia in 1 dog. Anemia (PCV $<$ 39%) was identified in 14/49 (28%) and hemo-concentration in 5/49 (10%) dogs. The most common serum biochemical findings were hyperbilirubinemia (49/49; median 70 μmol/L, range 6.6–646 μmol/L [4.1 mg/dL, range 0.40–37.8 mg/dL]), increased serum alkaline phosphatase activity (45/47; median 609 U/L, range 47–5,166 U/L), aspartate aminotransferase activity (45/49; median 368 U/L, range 34–13,356 U/L), alanine aminotransferase (ALT) activity (45/49; median 1,048 U/L, range 44–48,531 U/L), and gamma glutamyl transpeptidase activity (35/45; median 16 U/L range, 1–88 U/L). Hypoalbuminemia was present in 23/49 dogs (45%) and serum hypoglycemia in 10/49 (20%). Electrolyte abnormalities on presentation included hypokalemia in 13/45 (26%), hyperkalemia in 9/49 (18%), hypernatremia in 10/49 (20%), hyponatremia in 9/49 (18%), and hyperphosphatemia in 7/49 (14%). Blood ammonia concentration (median 146 μg/dL, range 0–1,080 μg/dL [86 μmol/L, range 0–634 μmol/L]) was determined in 11 dogs, and increased in 7 of these dogs (63%). Creatinine concentration (median 72 μmol/L, range 26.5–645 μmol/L [0.82 mg/dL, range 0.3–7.3 mg/dL]) was increased in 7/49 (15%) dogs. Plasma lactate concentration was increased in 21/29 (56%) dogs (median 3.6 mmol/L, range 0.6–15.7 mmol/L).

The PT and activated partial thromboplastin time (aPTT) were prolonged in all dogs at presentation and

Table 2: Selected variables at presentation in dogs with acute liver failure that did and did not survive

Variable	Survivors Median (range)	Number	Nonsurvivors Median (range)	Number	*P*-value	Reference range
Age (years)	2 (0.7–13)	7	6 (0.8–13)	42	0.585	NA
PCV (%)	43 (33–63)	7	45 (20–70)	42	0.765	39–55
WBC ($\times 10^9$/L [$\times 10^3/\mu$L])	17.5 (10–34)	7	17.3 (1.8–62)	34	0.579	4.9–16.9
Platelet ($\times 10^9$/L [$\times 10^3$ /μL])	192 (110–298)	7	139 (9–653)	43	0.549	180–524
PT (fold increase)	3.7 (1.6–6.5)	7	2.9 (1.5–6.5)	38	0.594	1.00
aPTT (fold increase)	2.00 (1.2–7.5)	7	1.67 (1.86–7.5)	38	0.612	1.00
Sodium (mmol/L [mEq/L])	146 (133–164)	7	146 (141–149)	42	0.876	140–150
Potassium (mmol/L [mEq/L])	4.2 (3.6–6.5)	7	4.1 (3–6)	42	0.197	3.7–5.4
Phosphate (mg/dL)	1.68 (1.4–1.9) [5.2 (4.6–6.1)]	7	1.64 (1.0–4.3) [5.1 (3.1–13)]	42	0.844	0.84–2.33 2.6–7.2
Lactate (mmol/L)	1.4 (0.8–8.1)	3	3.6 (0.6–16)	29	0.144	0–2
ALT (U/L)	1,446 (446–26,670)	7	901 (48–48,531)	44	*0.038*	14–86
AST (U/L)	964 (148–12,306)	7	378 (3,413,556)	42	0.249	9–54
ALP (U/L)	672 (347–3,009)	7	606 (47–5,166)	43	0.735	12–127
GGT U/L	15 (1–74)	7	13 (7–20)	45	0.654	0–10
Bilirubin (μmol/L [mg/dL])	67 (13.7–289) [3.9 (0.8–17)]	7	70 (6–2926) [4.1 (0.4–38)]	43	0.850	1.7–5.3 [0.1–0.3]
Glucose (mmol/L [mg/dL])	4.83 (3.5–5.9) [87 (63–107)]	7	4.55 (93.4–13.4) [82 (20–242)]	44	0.847	3.71–7.49 [67–135]
Cholesterol (mmol/L [mg/dL])	5.0 (2.0–12.3) [194(78–476)]	6	4.68 (0.96–19.0) [181 (37–734)]	33	0.792	2.12–8.76 [82–338]
Albumin (g/L [mg/dL])	31 (20–36) [3.1 (2.0–3.6)]	7	28 (12–42) [2.8 (1.2–4.2)]	42	0.134	28–40 [2.8–4.0]
Creatinine (μmol/L [mg/dL])	70 (27–513) [0.8 (0.3–7.3)]	7	75 (53–150) [0.85 (0.6–1.8)]	49	0.516	53–177 [0.6–2.0]

PT, prothrombin time; aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase.
Significance set at $P \leq 0.05$.

both parameters were out of the range in 12 dogs. Ancillary coagulation testing was done in 11 dogs. Hypofibrinogenemia was identified in 8/11 dogs (72%). Fibrin degradation products were >20,000 mg/L in 1/8 dogs and D-dimer concentrations were increased in 1/2 dogs.

Most dogs underwent diagnostic imaging procedures. Thoracic radiography was performed in 24 dogs and abnormalities noted in 8/24 (33%). Abnormal findings included pleural effusion (3/24, 13%), alveolar infiltrate (2/24, 8%) interstitial or bronchointerstitial infiltrate (2/24, 8%), and a mediastinal mass (1/24, 2%). Abdominal radiography was performed in 12 dogs. The most common abnormalities were loss of serosal detail in 7/12 (58%) and hepatomegaly in 3/12 (25%). Abdominal ultrasound was performed on 38 dogs (77%). The liver appeared normal in 8/38 (21%) dogs, inhomogeneous in 9/38 (24%), hypoechoic in 7/38 (18%), and hyperechoic in 4/38 (11%). Hepatomegaly was seen in 17/38 (45%) dogs and nodularity in 7/38 (18%). The gallbladder wall was thickened in 5/38 (13%) dogs and choleliths were present in 2/38 (5%). Abdominal effusion was present in 6/38 (16%) dogs and 1 dog had retroperitoneal effusion. Other findings on ultrasound included a thickened or edematous pancreas in 8/38 (21%) dogs, splenic thrombus in 1 dog, and a detectable gastric or colonic ulcer in 1 dog each.

Treatment

Due to abnormal coagulation parameters, 2 dogs received fresh frozen plasma (FFP), 4 dogs parenteral vitamin K[a] subcutaneously, and 11 dogs received a combination of both FFP and vitamin K. The median dose of FFP administered to these dogs was 15 mL/kg intravenously (range 9–70 mL/kg), while vitamin K was given at 0.5 mg/kg subcutaneously twice a day. PT and aPTT were rechecked 12–36 hours after these treatments, in 11 dogs receiving vitamin K or FFP and in 8 dogs receiving both treatments. Two dogs on vitamin K, 1 dog that received FFP, and 3 dogs that received both treatments had improvements in PT and aPTT while 1 dog each receiving vitamin K or FFP and 4/8 dogs receiving a combination had worsening of PT and aPTT prolongations. Three dogs were treated with a unit of packed red blood cells for clinical anemia. Other treatments included antimicrobial therapy in 42/49 dogs, gastroprotectants (famotidine,[b] 1 mg/kg intravenously q 24 or omeprazole,[c] 1 mg/kg orally q 24) in 12/49

(24%) dogs, intravenous *n*-acetylcysteine[d] (140 mg/kg intravenously once followed by 70 mg/kg intravenously q 6 h) in 12/49 (24%) dogs, ursodeoxycholate[e] (15 mg/kg orally q 24) in 7/49 (14%) dogs, and S-adenosylmethionine[f] (20 mg/kg orally q 24) in 6/49 (12%) dogs.

Secondary complications and concurrent diseases

Secondary complications were common. A progressive coagulopathy marked by hypocoaguability developed in many dogs. Evidence of hemorrhage was present in 25/49 (51%) dogs either based on clinical signs of bleeding ante-mortem or evidence of bleeding at necropsy. Fourteen dogs had melena, 7 had petechiation, 3 had bloody diarrhea, 4 had ecchymosis, 2 had hemoabdomen, 2 had hematuria, 2 had cerebral hemorrhage, and 1 each had adrenal hemorrhage or excessive bleeding from a catheter site. Four dogs had gastrointestinal ulceration, including 2 with gastric ulceration and 1 each with duodenal or colonic ulceration. Recheck of PT and aPTT in 21 dogs showed improvement in 10/21 (48%) dogs, with 5 of these returning to normal, deterioration in 8/21 (38%) dogs, and no change in 3 dogs. Of the 22 dogs with normal platelet count at admission, 9 were rechecked, and 6 of these became thrombocytopenic during hospitalization. Thus, overall 36/39 (92%) dogs with ALF had thrombocytopenia. Seven dogs met the criteria for a diagnosis of disseminated intravascular coagulation.[25]

Ascites was a frequently identified complication. Overall, 20/49 (41%) dogs had abdominal effusion detected either on physical examination, ultrasound, or at the time of necropsy. Fluid analysis was done antemortem in only 3 dogs; 2 of the effusions were neoplastic, and 1 was a modified transudate. At necropsy, 10 effusions were serosanguinous and 2 were hemorrhagic on gross evaluation. Five dogs had concurrent serosanguinous pleural effusion at necropsy. Of the 26 dogs with normal albumin concentrations at admission, 11 of them had albumin concentration rechecked, 6 of which developed hypoalbuminemia during hospitalization. Thus, 29/49 (59%) dogs developed hypoalbuminemia during hospitalization. In addition, 20/49 (41%) dogs had low total protein concentration (median 44 g/L, range 32–51 g/L [4.4 mg/dL, range 3.2–5.1 mg/dL]).

During the course of hospitalization, neurologic signs compatible with HE developed in 11 dogs, 6 of which developed seizures. Thus, including the 17 dogs that initially presented with neurologic signs, a total of 28/49 (57%) of dogs had signs compatible with HE in the study. Hypoglycemia was present in 11 dogs on admission and another 4 dogs developed hypoglycemia during hospitalization so that a total of 15/49 (31%) dogs were hypoglycemic. Of the dogs with hypoglycemia, all were treated with dextrose supplementation and 4 (27%) remained hypoglycemic.

Six out of 43 dogs had renal azotemia on presentation (defined by creatinine >176 μmol/L [2.0 mg/dL] in the face of dilute urine) and 2 more dogs developed anuric acute kidney injury during hospitalization. Both of these dogs had acute tubular necrosis on necropsy. Another 9 dogs had acute tubular necrosis at necropsy but were not azotemic. A clinical diagnosis of acute pancreatitis was made in 12 dogs based on ultrasound (thickened hypoechoic pancreas surrounded by hyperechoic fat) or histopathology of the pancreas at necropsy.

Statistical evaluation

The only presenting factor which predicted survival was high serum ALT activity ($P = 0.038$; Table 2). During hospitalization, predictors for mortality (Table 3) included a progressive increase in serum bilirubin concentration ($P = 0.05$) and a progressive decline in serum albumin concentration ($P = 0.009$) as well as the development of clinical bleeding ($P = 0.048$) or ascites ($P = 0.003$). The presence of moderate to marked hepatomegaly on ultrasound was associated with having hepatic neoplasia ($P = 0.001$).

Discussion

This retrospective study identified that dogs with ALF, defined by the acute onset of hepatic disease in combination with hyperbilirubinemia and coagulopathy, have a grave prognosis. Only 7/49 (14%) of the dogs survived to discharge. This survival rate is in accordance with that suggested in isolated case reports in dogs with toxic or infectious causes of ALF (0–37%),[9–11,19] and is similar to the survival rate (10–30%) reported for ALF in people in the absence of transplantion.[1–3]

The underlying cause for ALF was identified in only 18/49 (37%) of dogs in this study, the most common identified being neoplasia (13/49, 27%) with 11/13 (85%) round cell tumors. Lymphoma is also the most common infiltrative tumor causing ALF in people.[26] One distinctive finding in dogs with ALF due to hepatic neoplasia was the presence of moderate to marked hepatomegaly on ultrasound. In a previous case study of dogs with primary hepatic lymphoma (but not necessarily ALF), 81% of dogs had hepatomegaly.[27] Four of the 11 round cell tumors in this study were diagnosed with hepatic aspirate, suggesting that this relatively noninvasive technique is a valuable diagnostic tool in dogs with hepatomegaly and ALF. In addition, 2 cases in which coagulation parameters were severely prolonged were diagnosed by aspirate of palpably normal lymph nodes. Although the prognosis for hepatic lymphoma even in the absence of ALF is guarded in dogs and people,[26,27] 1 dog in the

Table 3: Selected variables in dogs with acute liver failure after hospitalization

Variable	Nonsurvivors		Survivors			
	Median (range)	Number	Median (range)	Number	*P*-value	Reference range
PCV (%)	36 (25–73)	25	28 (14–50)	7	0.87	39–55
ALT (U/L)	1,509 (269–7,161)	25	634 (19–3,507)	7	0.065	14–86
AST (U/L)	144 (51–717)	25	349 (28–5,834)	7	0.272	9–54
ALP (U/L)	641 (169–2,882)	25	1,058 (121–6,279)	7	0.381	12–127
Bilirubin (μmol/L [mg/dL])	22 (8.6–121) [1.3 (0.5–7.1)]	28	160 (3.4–991) [9.4 (0.2–58)]	7	*0.045*	1.7–5.3 [0.1–0.3]
Phosphate (mmol/L [mg/dL])	1.7 (1.5–2.0) [5.22 (4.6–6.1)]	28	1.9 (0.65–4.3) [5.9 (2.7–13.4)]	6	0.899	(0.84–2.3) [2.6–7.2]
Sodium (mEq/L)	148 (124–176)	28	146 (145–151)	6	0.98	140–150
Albumin (g/L [mg/dL])	31 (20–36) [3.1 (2.0–3.6)]	28	22 (13–38) [2.2 (1.3–3.8)]	7	0.009	28–40 [2.8–4.0]
Platelet ($\times 10^9$/L [$\times 10^3$/μL])	93 (22–147)	40	115 (11–365)	7	0.554	180–524
Creatinine (μmol/L [mg/dL])	88 (35–159) [1.0 (0.4–1.8)]	28	88 (35–592) [1.0 (0.4–6.7)]	7	0.541	53–177 [0.6–2.0]
Glucose (mmol/L [mg/dL])	4.8 (3.9–6.4) [87 (71–115)]	28	4.3 (1.6–9.4) [77 (28–169)]	7	0.221	3.7–7.5 [67–135]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.
Significance set at $P \leq 0.05$.

current study underwent chemotherapy and was still alive at the time of manuscript submission more than 1 year later.

A presumptive diagnosis of leptospirosis was made in 4 dogs (high acute titers with or without consistent histopathologic lesions), but only confirmed in the 1 dog that survived the 4 weeks until convalescent titers could be performed.[16] Although leptosporosis titers were not performed in all of the dogs in this study, the finding that this bacteria can cause ALF, sometimes in the absence of concurrent renal disease, suggests that testing for this infectious agent and empiric treatment with a penicillin antibiotic should occur in all dogs with ALF until convalescent titers are done or another diagnosis is confirmed.

Several dogs were administered drugs known to be involved in hepatotoxic reactions in dogs. These drugs included trimethoprim sulfa, carprofen, doxycycline, phenobarbital, and glucosamine.[4,6,15,21] Establishing with certainty if a hepatotoxic drug reaction has occurred can be challenging. A reputation as an established hepatotoxin, the temporal association between the clinical signs and drug administration, a response to drug withdrawal and a positive re-challenge are the criteria used to establish that a drug reaction has occurred.[28,29] In the setting of ALF, there may not be any response to drug withdrawal due to the severity of the hepatic insult and positive re-challenge is obviously unethical. These inherent difficulties in making a diagnosis of drug induced liver disease combined with the retrospective nature of this study made it difficult to definitely determine if a drug reaction was the cause of the ALF. Recognizing that a possible hepatotoxic drug reaction is occurring at the time a dog presents with ALF is critical, however, since prompt discontinuation of the drug is pivotal to the successful management of drug induced liver disease.[28,29]

Confirming an environmental toxin as a cause of ALF is difficult in veterinary medicine, as often the exposure is not witnessed, and clinicopathologic and histologic findings are not pathognomonic. One dog in this study was witnessed ingesting mushrooms, but it was unknown if they were mushrooms that produce amanitin. In some cases of intoxication, analysis of serum, urine, or gastric contents for known hepatotoxins (eg, aflatoxins, amantin, and microcystins) is possible.[30–32] This analysis, however, is not readily available and it is hard to obtain results in a timely manner. If toxin exposure is suspected, treatment with activated charcoal is indicated. In addition, for toxins that undergo enterohepatic circulation, the use of bile acid resins (ie, cholestyramine) may help to bind and eliminate the toxin.[20,33]

In people with Wilson's disease, an acute rise in cytosolic copper concentration can cause ALF with a concurrent acute hemolytic anemia.[34] Unlike chronic hepatic copper toxicity, acute copper toxicity can be diagnosed by demonstrating high serum and urinary copper concentrations as well as by the demonstration of excess copper staining in hepatic aspirates or biopsy.[34] Copper analysis was not done in any of the dogs in this current study. In a previous study of dogs with acute hepatitis, copper staining was increased on histopathology in several dogs.[23] Thus, in dogs with ALF, copper

toxicosis should be considered as a possible etiology, especially in breeds known to accumulate excess copper in their liver. Serum copper analysis or staining for copper stores in hepatic tissue should be undertaken in all dogs diagnosed with ALF. In people, ALF from Wilson's disease has a grave prognosis for spontaneous recovery without transplant.[34] The prognosis in dogs with acute hepatic copper toxicity has not been defined.

One factor that contributed to the high percentage (63%) of dogs without a definitive diagnosis in this study was the fear that attempting hepatic biopsy would provoke bleeding. Only 5/49 (10%) of dogs had a hepatic biopsy with an additional 6 undergoing fine-needle aspiration. This ante-mortem evaluation of hepatic tissue established a diagnosis of cancer in 5/11 (45%) of dogs. Most of the histopathological specimens, however, were evaluated post-mortem. With the exception of cancer, the histopathological lesions identified at necropsy in the liver of most dogs were not indicative of a specific etiology. The most common findings were degenerative changes such as necrosis and lipidosis. Three dogs had primary inflammatory lesions that could have been compatible with an immune hepatitis. In people, autoimmune hepatitis can present as ALF and some of these patients respond to corticosteroids.[35] However, recent evidence suggests that even in the face of a known immune disorder administration of corticosteroids to patients with ALF may be detrimental.[35] Whether it is appropriate to try a course of corticosteroids in dogs with ALF in the face of an inflammatory biopsy is unknown.

Several variables were associated with nonsurvival in this small retrospective study. These factors primarily reflected progressive hepatic dysfunction such as increasing serum bilirubin and decreasing serum albumin. Curiously, higher ALT activity at presentation was associated with survival. This could reflect the fact that more hepatocytes were initially viable in survivors so there was more ALT to leak or alternatively that the dogs with exposure to toxins, such as aflatoxin or microcystin that inhibit ALT, were more likely nonsurvivors. Alternatively, this finding may represent a Type 1 statistical error.

The development of ascites was a common complication in the dogs in this study and was associated with nonsurvival. Ascites in these cases may have been secondary to increased intravascular hydrostatic pressure, as from portal hypertension or large fluid volume administration; to decreased intravascular oncotic pressure due to hypoalbuminemia; to excessive vascular leak due to vasculitis, regional peritonitis, or systemic inflammatory response syndrome; to neoplasia; or to a combination of these factors. We did note a decrease in total plasma protein concentration in the dogs over time and this may have contributed to the development of ascites. In addition, volume overload from administration of large volumes of fluids and blood products could have promoted the development of ascites. Ascitic fluid leading to development of an abdominal compartment syndrome,[36] in turn, could have contributed to neurologic deterioration (from increased intracranial pressure) or the development of acute tubular necrosis (from reduced renal perfusion) or gastrointestinal ulceration and hemorrhage (from edema and tissue trauma). The practice of indiscriminate use of blood products to correct abnormalities in PT and aPTT in ALF patients that are not bleeding should be discouraged. In an American Association for the Study of Liver Disease consensus statement on ALF in people, blood product replacement therapy for prolonged PT is recommended only in the setting of active hemorrhage or prior to invasive procedures.[2]

The clinical course of dogs with ALF in this study was typically rapidly progressive and fatal. It was marked by ongoing deterioration of hepatic function with development of a progressive coagulopathy and encephalopathy along with gastrointestinal and renal dysfunction. Although not all dogs had neurologic signs at the time of presentation, during the course of hospitalization 57% of the dogs were diagnosed with signs consistent with HE. Neurologic signs included progressive lethargy advancing to stupor and coma. In addition, 6 dogs had seizures during the course of their disease. These progressive neurologic signs developed despite the institution of medical therapy for HE including lactulose and metronidazole in many dogs. The acute HE of ALF, unlike the chronic HE seen in dogs with congenital portosystemic shunts, responds poorly to the administration of nonabsorbable disaccharides, antimicrobials, and feeding protein-restricted diets.[37–39] This poor response reflects the difference in pathophysiology. The HE associated with ALF involves the development of acute cerebral edema and intracranial hypertension and is complicated by hypoglycemia and hyponatremia. In people with ALF, intracranial pressure is often monitored and measures to decrease intracranial pressure such as elevation of the head, control of systemic hypertension and minimization of agitation and pain are standard of care for patients with ALF.[38] If increased pressure is suspected, mannitol administration, induced hypothermia, and barbiturate anesthesia with mechanical ventilation may also be used as therapy. Dogs in this study were not routinely monitored or treated for potential cerebral edema or an increase in intracranial pressure. Studies that assess the impact of measures to minimize increases in intracranial pressure in on the development of encephalopathy in dogs with ALF are warranted.

Many dogs in the current studies developed progressive bleeding tendencies which were associated with

nonsurvival.[40] Despite prolongation of PT and aPTT in all dogs at presentation, there was actually little evidence of spontaneous bleeding at that time. Perhaps early in the course of the development of hepatic failure deficiencies in procoagulants are balanced by the concurrent deficiency of anticoagulants. Indeed, low antithrombin and protein C activity have been demonstrated in dogs with ALF.[9,41] In this study, as progressive decreases in hepatic function occurred, manifested as higher serum bilirubin and lower serum albumin concentrations, clinical bleeding developed as evidenced by gastrointestinal bleeding, hemoabdomen, and the presence of cutaneous petechiation. The presence of ongoing hemorrhage was also reflected in the development of progressive anemia and thrombocytopenia and the findings of occult internal hemorrhages in the liver, peritoneal space, bladder, and adrenals on necropsy examination. Unexpectedly, the development of bleeding was not always accompanied by progressive prolongations of PT and aPTT. In people undergoing liver transplantation, serum fibrinogen concentration and thromboelastography are successfully used to predict bleeding.[42] Although only 11 dogs in this study had serum fibrinogen measured, 5/8 had clinical evidence of bleeding.[42] Preliminary results from our coagulation laboratory using thromboelastography suggest that dogs with ALF do indeed develop hypocoagulable tracing many with concurrent hyperfibrinolysis.[43] Additional studies to characterize the state of coagulation in dogs with ALF are needed.

Many dogs had histopathologic lesions in organs other than the liver. Acute tubular necrosis was observed histopathlogically in 11 dogs, and manifested as clinical acute kidney injury in 2 of the dogs, both of whom became anuric. Whether the renal lesions were a consequence of ALF or secondary to the same toxin or infectious agent that caused the liver injury is unknown. Acute necrotizing and hemorrhagic pancreatitis was present in 3 dogs. In addition, gastric or intestinal ulceration was documented on necropsy in 3 dogs. Damage of the gastrointestinal tract could have been due to concurrent toxicosis, from hypotension, or abdominal compartment syndrome secondary to ascites.[36]

There were several limitations to this study. The retrospective nature of the study resulted in missing data points for several clinicopathological parameters and complicated detection of signs of HE and discernment of whether a hepatotoxic drug reaction had occurred. In addition, the presence of perceived hypocoagulability prevented the acquisition of ante-mortem hepatic histopathology. Furthermore, the dogs received widely varying treatment regimens. Lastly, since most dogs died it was difficult to identify prognostic indicators.

Conclusions

Canine ALF is associated with a grave prognosis. Strategies to increase survival are urgently needed. The current study suggests that besides targeting deteriorating hepatocellular function with specific antidotes and supportive care strategies, better characterization of the coagulopathy associated with ALF and strategies to prevent the development of ascites, gastrointestinal, and renal dysfunction are warranted.

Footnotes

[a] Aqua-mephyton, vitamin K, Merck and Co, Kenilworth, NJ.
[b] Pepcid, famotidine, McNeil Consumer Pharmaceuticals, Fort Washington, PA.
[c] Prilosec, omeprazole, Procter and Gamble, Cincinnati, OH.
[d] Acetadote, Cumberland Pharmaceuticals, Nashville, TN.
[e] Ursodeoycholate, LGM Pharmaceuticals, Nashville, TN.
[f] Denosyl, s-adenosylmethionine, Nutramax, Edgewood, MD.

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