Acute pancreatitis: a newly recognised potential complication of canine babesiosis

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ABSTRACT

This retrospective study describes 4 cases of canine babesiosis with histologically confirmed acute pancreatitis. In addition, 16 dogs with babesiosis are reported with serum amylase (>3500 U/ℓ) and/or lipase (>650 U/ℓ) activity elevations of a magnitude that would support a diagnosis of probable acute pancreatitis, although extra-pancreatic sources of the enzymes could not be excluded in these cases. Median time of pancreatitis diagnosis was 2.5 days post-admission, with primarily young (median age 3 years), sexually intact dogs affected. The development of pancreatitis was unrelated to the degree of anaemia at time of admission. In addition to pancreatitis, 80 % of cases suffered from other babesial complications, namely icterus (13), acute respiratory distress syndrome (6), immune-mediated haemolytic anaemia (6), renal failure (3), haemoconcentration (2) and cerebral syndrome (2). Acute respiratory distress syndrome, renal failure and cerebral syndrome were associated with a poor prognosis, with 4 of the 5 dogs included in the overall 26 % mortality rate having at least 1 of these complications. Haemolytic anaemia with ischaemia-reperfusion injury to the pancreas is proposed as a possible primary pathophysiological mechanism in babesial pancreatitis. Hypotensive shock, immune-mediated haemolytic anaemia, haemoconcentration and possibly altered lipid metabolism in babesiosis may also be involved. The previously postulated pro-inflammatory cytokine milieu of complicated babesiosis may underlie the progression, if not the primary initiation, of pancreatic pathology. Acute pancreatitis may represent the previously reported 'gut' form of babesiosis.

Key words: amylase, *Babesia canis,* dog, lipase, multiple organ dysfunction syndrome, pancreatitis.

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INTRODUCTION

Canine babesiosis is a tick-borne disease caused by the haemoprotozoan parasite *Babesia canis*[53]. Different isolates of *B. canis* are capable of inducing differing disease syndromes[46]. Babesiosis in South Africa is caused by *B. canis rossi*[46,53]. Haemolytic anaemia due to both intravascular and extravascular haemolysis is the hallmark of babesiosis[32]. The disease can be divided clinically into uncomplicated babesiosis, where clinical signs are attributable to the anaemic state alone, and complicated babesiosis, where additional factors are thought to play a role in disease expression[25]. Well-recognised complications of *B. canis* infection include acute renal failure, cerebral syndrome, icterus and hepatopathy, immune-mediated haemolytic anaemia (IMHA), pulmonary oedema (attributed to the acute respiratory distress syndrome (ARDS)), shock, coagulopathy and disseminated intravascular coagulation (DIC), peracute babesiosis, and the haemoconcentrated form of the disease[25]. Although single-organ dysfunction usually predominates in complicated babesiosis, multiple organs may be affected in many animals (C Welzl, Veterinary Medical University of Vienna, pers. comm., 1999).

The similarities between complicated *B. canis* symptomatology and human falciparum malaria have been recognised for decades[33], with both diseases being characterised by severe haemolytic anaemia, and sharing very similar complications[9,25]. The variety of complications and pathology cannot, however, be attributed to the anaemia-induced hypoxaemic state alone[9,30], and it has recently been proposed that development of the systemic inflammatory response syndrome, with progression to the multiple organ dysfunction syndrome, may underlie the complicated forms of both these diseases. The current widely-accepted view is that the different complications and multiple organ dysfunctions are caused by the effects of an unfocused and excessive host inflammatory response, rather than by the parasite itself[9,25]. The most important mediators of this response are thought to be cytokines, nitric oxide, free oxygen radicals, eicosanoids and platelet-activating factor[25]. Tumour necrosis factor-α and nitric oxide have recently been demonstrated to contribute to the pathogenesis of *B. caballi* infection in horses[21], and acute human babesiosis has similarly been suggested to share similarities with the immune response of human malaria[47].

Canine acute pancreatitis (AP) is a complex condition with numerous precipitating and predisposing risk factors[49]. These include infection[20,45,50], vascular disorders (vasculitis[45,50,57], thromboembolism[45], hypotension[45,57]), nutrition[20,45,50], shock[20,50,57], abdominal trauma[45,50] or surgery[20,45], hypercalcaemia[20,45,50], pancreatic duct obstruction[45], thoracolumbar neurosurgery[20], hyperlipidaemia[20,45,50] and putatively also drugs (including glucocorticoids, azathioprine, oestrogens, tetracyclines, chlorpromazine, furosemide, sulphonamides, and chlorthiazides)[11,20,45,50]. Over 60 % of dogs with AP have been found to suffer from concurrent disease[11].

Acute pancreatitis is described as a newly-identified potential complication of *B. canis* infection in dogs.

MATERIALS AND METHODS

A retrospective study was performed using patient records from the Department of Companion Animal Medicine, Faculty of Veterinary Science, University of Pretoria. All dogs with naturally occurring babesiosis that were admitted to the Onderstepoort Veterinary Academic Hospital (OVAH) between January 1996 and February 1999, and had serum amylase (AMS) and/or lipase (LIP) activities determined, were evaluated. Babesiosis was diagnosed in all cases on a thin capillary blood smear, stained with a rapid Romanowski-type stain (CAMS Quik stain; C A Milsch).

Serum AMS activity (Trace Scientific, Melbourne, Australia) was determined by

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Table 1: **Patient data for 20 dogs with acute pancreatitis as a potential complication of babesiosis.**

Dog	Breed	Age	Sex	Weight (kg)	Day[a]	Admission haematocrit (ℓ/ℓ)	Haematocrit at time of pancreatitis diagnosis	Known complications	Outcome
1*	Airedale	6 y	M	17	3	0.54	0.37	ARDS, CNS, HC	Died
2*	Pit bull-terrier	5 y	F	NK	NK	NK	0.15	IC	Euthanased
3**	Miniature dobermann	NK	F	NK	0	0.28	0.28	IC, IMHA, ARDS, CNS	Died
4**	Pekingese	12 y	F	6	2	NK	0.34	IC, IMHA, ARDS, RF	Died
5	Bull-terrier	4.5 y	F	21	5	0.09	0.13	IC, IMHA	NK
6	Bull-terrier	4 m	M	10	NK	0.10	NK	IC, ARDS	Survived
7	Chihuahua	9 y	F	3	2	0.11	0.28	IC	Survived
8	Boerboel	7 m	M	33	3	0.11	0.23	IC	Survived
9	Crossbreed	5 y	F	8	3	0.12	0.20	IC	Survived
10	Miniature dobermann	7 y	F	5	2	0.16	0.20	IC, IMHA	Survived
11	Maltese	6 y	F	5	5	0.22	0.20	IC, IMHA	Survived
12	Crossbreed	3 y	M	9	0	0.32	0.32	None	Survived
13	Rottweiler	1.8 y	F	NK	1	0.32	0.31	None	Survived
14	Maltese	8 y	F	32	15	0.33	0.13	IMHA	Survived
15	Bassett	2 y	M	8	5	0.49	0.44	HC	Survived
16	Bull-terrier	1 y	M	15	NK	0.07	NK	IC, ARDS	Survived
17	Pekingese	7 y	M	NK	NK	0.09	NK	IC, RF	Died
18	German shepherd	3 y	F	37	2	0.16	0.27	None	Survived
19	Labrador	4 m	M	14	5	0.17	0.21	None	Survived
20	Bullmastiff	3 y	F	49	2	0.18	0.22	IC, ARDS, RF	Survived

NK = not known; IC = icterus; ARDS = acute respiratory distress syndrome; RF = renal failure; IMHA = immune-mediated haemolytic anaemia; CNS = cerebral babesiosis; HC = haemoconcentration.
[a]Number of days between diagnosis of babesiosis and diagnosis of AP.
*Acute pancreatitis diagnosed both histologically and on amylase and lipase diagnostic criteria.
**Acute pancreatitis diagnosed histologically, without satisfying amylase and lipase diagnostic criteria.

a chromogenic, blocked PNP-heptaoside substrate modification by the method described by Foo *et al.*[16]. Serum LIP activity (Boehringer Mannheim, Mannheim, Germany) was determined with modification of the triolein turbidity method, using previously described methods[37,54,60].

Acute pancreatitis was definitively diagnosed in cases where necropsy examination and histopathology confirmed AP, irrespective of serum AMS and/or LIP activities. For the purposes of this study, a diagnosis of probable AP was defined as a serum AMS activity greater than twice top-normal values (>3600 U/ℓ), and/or a serum LIP activity exceeding 3.25 times top-normal values (>650 U/ℓ), in combination with supportive clinical signs. These AMS and LIP cut-off values have been shown to have a diagnostic efficiency of 90 % for AP[40]. Since azotaemia decreases the specificity of AMS and LIP activity elevations for a diagnosis of AP[40], linear regression statistical analysis (SigmaStat, Jandel Scientific Software) was performed in all the azotaemic dogs (serum creatinine >133 µmol/ℓ) to correlate the degree of AMS and LIP activity elevation with the degree of creatinine elevation. A statistically significant correlation was defined as a power of the performed test of ≥0.8. Serum trypsin-like immunoreactivity (TLI) was not assessed.

The degree of anaemia at the times of presentation and of AP diagnosis was classified as follows[41]: dogs with a haematocrit of <0.15 ℓ/ℓ were considered severely anaemic, those with haematocrits of 0.15–0.29 ℓ/ℓ were classified as moderately anaemic, and those with haematocrits ≥0.30 ℓ/ℓ were considered non-anaemic.

Concurrent babesial complications were defined as follows:

1. Acute respiratory distress syndrome: dyspnoea and radiographic pulmonary oedema, and/or PaO_2 <60 mmHg.
2. Renal failure: serum creatinine >150 µmol/ℓ and oliguria (<1 mℓ/kg/hour); not resolved by rehydration.
3. Immune-mediated haemolytic anaemia: positive in-saline erythrocyte agglutination.
4. Haemoconcentration: haematocrit >0.47 ℓ/ℓ in conjunction with congested mucous membranes and severe intravascular haemolysis.
5. Cerebral babesiosis: central neurological signs not attributable to any other known cause.
6. Icterus: yellow discolouration of oral and/or ocular mucous membranes.

RESULTS

Serum AMS and/or LIP activities were determined for 76 dogs with babesiosis admitted to the OVAH over a 38-month period. Eighteen of these dogs satisfied the diagnostic criteria of probable AP (AMS > 3500 U/ℓ and/or LIP > 650 U/ℓ)[40]. Two of these (Dogs 1 and 2) also had AP confirmed histologically. In addition to the above 18 dogs, AP was confirmed in 2 (Dogs 3 and 4) on histological necropsy examination, without satisfying the AMS and LIP inclusion criteria (Tables 1, 2).

All 12 female dogs were unspayed, while only 1 of the 8 male dogs had been castrated. Twelve dogs (63 %) were ≤5 years of age, with 42 % (8/19) of dogs being ≤3 years old (median age = 3 years; range = 4 months to 12 years).

Of the 16 dogs for which data were available, AP was diagnosed on the day of admission in 2 dogs, and on Days 1 (1 dog), 2 (5 dogs), 3 (3 dogs), 5 (4 dogs), and 15 (1 dog) after admission to the OVAH. The last dog had suffered a protracted illness characterised by intermittent anorexia and vomition for the 15 days before AP diagnosis. The median time of AP diagnosis was 2.5 days post-admission.

Clinical signs that prompted the investigation of possible concurrent AP were anorexia (100 % of cases), vomition (88 %), melaena (44 %), abdominal pain (41 %), diarrhoea (25 %), abdominal effusion (12 %), haematemesis (1 dog) and severe intractable ileus (1 dog). Abdominal survey radiographic findings compatible with AP included a fluid-filled pylorus and small intestinal gas distention (up to 3.5 rib widths) in the single case (Dog 1) for which radiographs were taken. Diagnostic abdominal ultrasound examination demonstrated hyperechoic peri-pancreatic mesenteric fat in Dog 4.

At time of admission, 7 dogs were

Table 2: **Serum biochemical values for 20 dogs with acute pancreatitis as a potential complication of babesiosis.**

Dog	Amylase[a] (U/ℓ)	Lipase[a] (U/ℓ)	Urea (mmol/ℓ)	Creatinine (µmol/ℓ)	Alkaline (U/ℓ) phosphatase	Alanine (U/ℓ) transaminase	Potassium (mEq/ℓ)
Normal[b]	200–1800	10–200	3.6–8.9	40–133	40–190	5–40	3.6–5.1
1*	4180	1216	14	103	180	52	3.2
2*	4042	2816	18	37	ND	ND	2.3
3**	ND	ND	ND	ND	ND	ND	ND
4**	ND	471	22	ND	377	28	2.8
5	3257	7255	8	ND	157	71	2.4
6	4289	1261	ND	42	125	183	2.7
7	6409	929	50	82	ND	ND	2.7
8	17857	975	13	23	ND	ND	3.2
9	8132	501	5	67	690	46	2.7
10	1718	2315	5.3	ND	1089	535	3.3
11	3029	8470	7	108	180	1310	3.8
12	6748	1732	6	87	ND	ND	ND
13	5265	1094	25	75	61	78	4.2
14	2748	1754	22	86	1925	373	ND
15	739	747	4.4	74	49	45	5.2
16	3907	627	31	147	335	90	3.8
17	3398	1236	ND	173	335	610	ND
18	3178	3519	13	154	290	51	4.8
19	21095	34740	45	249	346	1095	3.6
20	8825	1700	51	308	ND	ND	3.2

ND = not determined.
[a]Diagnostic criteria for probable acute pancreatitis: amylase >3600 U/ℓ and/or lipase >650 U/ℓ.
[b]Reference values: biochemistry laboratory, Section of Clinical Pathology, Department of Companion Animal Medicine, University of Pretoria.
*Acute pancreatitis diagnosed both histologically and on amylase and lipase diagnostic criteria.
**Acute pancreatitis diagnosed histologically, without satisfying amylase and lipase diagnostic criteria.

severely anaemic, 6 dogs were moderately anaemic, and 5 dogs were non-anaemic. Two of the non-anaemic dogs (Dogs 1 and 15) suffered from haemoconcentrated babesiosis, both having admission haematocrits ≥0.47 ℓ/ℓ. At the time of AP diagnosis, 2 dogs were severely anaemic, 10 dogs were moderately anaemic, and 5 dogs were non-anaemic. Only 3 dogs had a haematocrit of less than 0.20 ℓ/ℓ at the time of AP diagnosis. Whole blood transfusion had been administered to 50 % (8/16) of dogs. One dog from the transfused group, and 1 from the non-transfused group died.

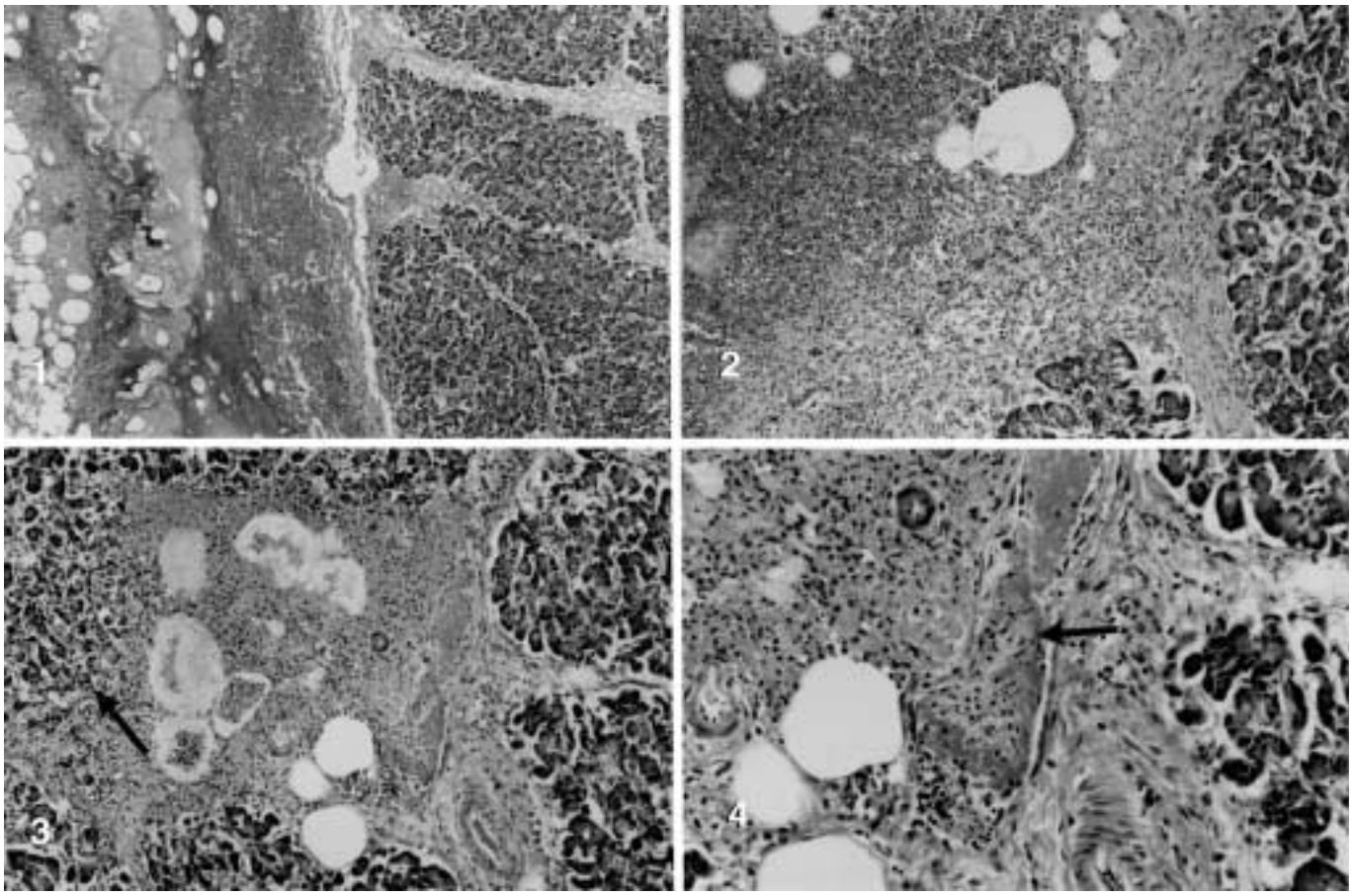
Eighty percent (16/20) of dogs had concurrent babesial complications in addition to AP, namely clinical icterus (13 dogs; 65 %), ARDS (6 dogs; 30 %), IMHA (6 dogs; 30 %), renal failure (RF; 3 dogs; 15 %), haemoconcentration (2 dogs; 10 %), and cerebral syndrome (2 dogs; 10 %). Only 4 dogs had AP as a single known complication of babesiosis.

Icterus was present in all (7/7) dogs with severe anaemia, 67 % (4/6) of dogs with moderate anaemia, and none of the non-anaemic dogs. Serum alkaline phosphatase (ALP) activity was elevated in 60 % (3/5) of the severely anaemic dogs, 75 % (3/4) of moderately anaemic dogs, and 25 % (1/4) of non-anaemic dogs. Serum alanine transaminase (ALT) activity was elevated in 93 % (13/14) of dogs. Hepatic function tests were performed on 4 dogs. Fasting serum bile acid concentrations were elevated in all 3 of the severely anaemic dogs (190 µmol/ℓ in Dog 16, 36 µmol/ℓ in Dog 17, and 13 µmol/ℓ in Dog 6; reference range <5 µmol/ℓ)[8], and normal in the only non-anaemic dog (Dog 13) for which it was assessed. Hypokalaemia (range: 2.3 to 3.3 mEq/ℓ) was identified in 63 % (10/16) of dogs. Of the icteric dogs, 69 % (9/13) were hypokalaemic, while only 1 of the non-icteric dogs was marginally hypokalaemic.

Elevated serum creatinine concentration was present in 5 cases (Dogs 16–20). Linear regression statistical analysis revealed only a very weak correlation between both creatinine and LIP activities (power of the test = 0.072), and creatinine and AMS activities (power of the test = 0.166), for these 5 dogs. Serum urea concentrations were disproportionately elevated in comparison to creatinine in 10/14 (71 %) of dogs for which both were determined.

Antibabesial chemotherapy was administered at the time of admission, using diminazene (Berenil, Hoechst Roussel) in 18 dogs, and trypan blue (Trypan blue, Kyron Laboratories) and imidocarb dipropionate (Forray-65, Schering-Plough AH) in 1 dog each. Corticosteroids had been administered on at least 1 occasion to 40 % (8/20) of dogs before the development of AP. Three of these dogs received a single intravenous bolus of dexamethasone at the time of presentation, while the remaining 5 dogs received oral prednisolone (2 mg/kg, once or twice daily) as immunosuppressive treatment for concurrent IMHA. The duration of such treatment before AP diagnosis was 1 day (2 dogs), 2 days (1 dog), 4 days (1 dog), and 5 days (1 dog).

Treatment of AP was in accordance with treatment recommended in standard texts[59]. Seventy-four percent (14/19) of dogs survived, while 21 % (4/19) died naturally and 1 dog was euthanased (for unspecified reasons). Necropsy and histology results were available for 4 (Dogs 1–4). Gross lesions of AP were seen in all 4 necropsied dogs. The pancreas were mildly swollen and contained scattered parenchymal haemorrhages, accompanied by multifocal or widespread pancreatic, peripancreatic, and mesenteric fat necrosis. Histology of the pancreas in 3 dogs (Dogs 1, 3, and 4) revealed interstitial and stromal oedema (Fig. 1). Focal to multifocal (Dog 2) or diffuse (Dogs 1, 3, and 4) necrosis of pancreatic and peripancreatic adipose tissue was associated with neutrophil infiltration of variable intensity, fibrin exudation, vascular necrosis and thrombosis, and occasional haemorrhage (Figs 1–4). Necrosis of the pancreatic parenchyma was limited to the periphery of some of the lobules bordering areas of fat necrosis and acute inflammation (Fig. 3). In addition to lesions referable to uncomplicated babesiosis, several dogs had necropsy findings that supported clinical manifes-



Figs 1–4. 1: **Pancreas and mesenteric fat. Extensive peripancreatic fat necrosis and acute inflammation** (on left of photograph)**, with interstitial pancreatic oedema** (on right)**.** HE, ×20. 2: **Pancreas. Higher magnification of Fig. 1, illustrating peripancreatic fat necrosis accompanied by the infiltration of large numbers of neutrophils** (on left of photograph)**.** HE, ×100. 3: **Pancreas. Focal pancreatic fat necrosis with acute interstitial inflammation. Note parenchymal necrosis** (arrow) **bordering the areas of interstitial necrosis and inflammation.** HE, ×100. 4: **Pancreas. Higher magnification of Fig. 3: demonstrating vascular thrombosis** (arrow) **in the area of interstitial necrosis and inflammation.** HE, ×300.

tations of complicated babesiosis. These included icterus (4/4 dogs); acute interstitial pneumonia (ARDS; 3/4); and multifocal mid-brain haemorrhage (cerebral babesiosis; 1/4).

DISCUSSION

This study describes 4 cases of canine babesiosis with histologically confirmed AP. In addition, 16 dogs with babesiosis are reported with serum AMS and/or LIP activity elevations of a magnitude considered sufficient for the presumptive clinical diagnosis of AP (AMS >3500 U/ℓ and/or LIP >650 U/ℓ)[40]. Owing to the retrospective nature of the study, these presumptive diagnoses of AP remained histologically unconfirmed, and the term probable AP is used for these 16 cases.

The 'gold standard' for the definitive antemortal diagnosis of AP is pancreatic biopsy[20], and pancreatic histopathology has recently been used as an inclusion criterion in papers dealing with canine AP[22,23]. However, these papers described fatal AP, and pancreatic tissue was thus available for evaluation in all cases. In the clinical setting, critically ill dogs suffering from complicated babesiosis are poor anaesthetic candidates, and surgical pancreatic biopsy is not performed diagnostically. Laparoscopic pancreatic biopsy could be considered in these cases, but this technique requires anaesthesia and is not routinely performed at the OVAH.

Elevated serum AMS and/or LIP activities, in combination with supportive clinical signs and clinicopathologic variables, have long been considered diagnostic for AP in dogs, and have served as the main inclusion criteria in previous publications on canine AP[11,40,45,50]. Such elevation of AMS and LIP activities is, however, not specific for a diagnosis of AP. Extrapancreatic disease that may potentially lead to elevated serum AMS and/or LIP activities include duodenal foreign bodies[58], neoplasia[45], azotaemia[40] and hepatic[45] or gastric disease[7]. However, none of the dogs in the present study suffered from intestinal foreign bodies or known neoplasia. Five of the 16 dogs with a diagnosis of probable AP were azotaemic at the time of sampling. Linear regression analysis correlating the degree of azotaemia with the extent of AMS and LIP elevation in these 5 dogs showed only a very weak correlation, also rendering azotaemia unlikely to have led to false positive diagnoses of AP. Hepatic or gastrointestinal sources of AMS and LIP could, however, not be excluded, which may have led to the erroneous diagnosis of probable AP in some of these 16 cases. Despite the limitations of the current study, the magnitude of elevation of AMS and LIP activities, in combination with the classical clinical and clinicopathologic features of AP exhibited by these dogs, supports the diagnosis of probable AP in these patients.

Approximately 1250 cases of canine babesiosis are annually presented to the OVAH, of which 31.4 % (approximately 393 dogs per year) are considered ill enough to warrant admission to the hospital[48]. During the 38-month study period, approximately 1245 cases of canine babesiosis were admitted to the OVAH. Excluding the 16 cases of probable AP in this study, the incidence of histologically confirmed AP in the canine population with babesiosis admitted to the OVAH during this period was at least 0.32 % (4/1245). This is comparable to an incidence of canine AP of at least 0.04 % in our general hospital population[40].

In addition to the 20 dogs included in

this study, 58 further dogs with babesiosis were identified during the study period that were suspected clinically to have AP, but these dogs did not meet the AMS and LIP inclusion criteria. **N**ormal serum AMS and/or LIP activities may, however, accompany AP[20] in as many as 13–20 % of dogs[11,50], and high serum AMS or LIP activities occurred in only 69 % and 39 %, respectively, in a recent case series of fatal canine AP[23]. Owing to the low predictive value of a negative result based on AMS and LIP quantification, and the fact that the extent of serum AMS or LIP activity elevation does not reflect the severity of disease[20], it is possible that the incidence of AP in babesiosis may in fact be greater than that reported in this study.

Serum discolouration may also affect the determination of amylase and lipase activities. Lipaemia may falsely reduce amylase[10,14] and lipase[14] activities, while hyperbilirubinaemia may falsely decrease serum lipase activity[14]. The lipaemic (4) and icteric (7) sera in the present study may therefore have led to an underestimation of serum AMS and/or LIP activities. Haemolysis may falsely decrease serum lipase activity[14], but may result in falsely elevated amylase activities[10,14]. In the present study, mild haemolysis was seen in only 2 samples at the time of AMS and LIP determinations, rendering haemolysis unlikely to have led to falsely elevated serum amylase levels.

Acute pancreatitis is reportedly most prevalent in middle-aged to old[23,45], spayed or castrated[11], and obese female dogs[45], with dogs greater than 7 years of age being at an increased risk[11]. The patient profile of the dogs in the current study differs from the above in that all 12 females and all but 1 of the 8 male dogs were sexually intact, and predominantly young dogs were affected, with 63 % of dogs being ≤3 years old (median age 3 years). Commonly reported clinical signs of AP include anorexia, vomition, diarrhoea, abdominal pain, melaena, haematemesis and haematochesia[20,59], similar to this study. Abdominal ultrasonography is a valuable diagnostic aid in canine AP[23], and ultrasonographic manifestations compatible with AP were seen in the only dog in the present study on which ultrasound diagnosis was performed. Owing to the difficulties associated with the clinicopathological diagnosis of AP, this modality may in future prove to be of further benefit in the diagnosis of babesial pancreatitis.

Progressive physiologic failure of several interdependent organ systems, rather than the underlying disease or a single complication thereof, has been identified as a major threat to survival in patients with life-threatening illness[4]. Secondary multiple organ failures usually evolve after a latent period following the inciting injury[4], with delayed organ dysfunction manifesting after the patient has already appeared to recover[25]. This was the general pattern of disease progression in most of our patients, and AP in babesiosis may be considered a delayed organ failure.

Serum ALT was elevated in 93 % of the dogs in this study, in contrast to the previously reported 25–41 % in babesiosis[41], and icterus was also more common (65 %) than the previously reported 40 % in complicated babesiosis[25]. These changes may reflect additional hepatic compromise secondary to AP. Hepatic enzyme elevations in canine babesiosis have been attributed to hypoxic hepatopathy[41], which is characterised histologically by varying degrees of centrilobular congestion and necrosis[25]. Similarly, in the present study, an increased incidence of raised serum ALP, icterus, and abnormal hepatic function tests was seen in the anaemic dogs, as compared to the non-anaemic dogs, which may therefore be a reflection of haemolysis and hypoxia. However, in addition to this hypoxic hepatopathy, acute pancreatitis may also lead to ALT and ALP elevations and icterus, secondary to inflammatory hepatocellular injury (hepatic necrosis, loss of normal architecture, and fatty infiltration) and/or cholestasis[20,45]. Compromised gut-barrier function with bacterial translocation from the gastrointestinal tract to the portal system may also occur in AP[35], contributing to the hepatopathy. The high incidence of icterus in our study agrees with previous observations that icterus is associated with other babesial complications in the majority of cases, and rarely occurs as an isolated complication[25]. It has also been described that recovery in icteric dogs may be delayed, in comparison to non-icteric cases[25], which was also seen in our study. Although based on a small number of cases, the presence of icterus may therefore support the clinical suspicion of AP in a dog with suggestive clinical signs and clinicopathologic findings. Of the icteric dogs, 69 % were hypokalaemic, while only 1 of the non-icteric dogs was marginally hypokalaemic. A causal link between icterus and hypokalaemia is, at present, lacking. Disproportionate elevations of serum urea in comparison to creatinine concentrations in 71 % of our cases could be attributed to haemoglobin degradation in babesiosis[41], a generalised catabolic state as described in sepsis, or a reflection of gastrointestinal haemorrhage secondary to AP, since melaena was present in 44 % of our cases, and haematemesis occurred in 1 dog.

Canine babesiosis shares many similarities with human falciparum malaria, and it has been suggested that the 2 diseases share common pathophysiological mechanisms[25,41]. Acute pancreatitis has been described as an uncommon complication of falciparum malaria in isolated case reports since 1988[13,19,27,44,52,55]. The development and diagnosis of AP occurred 3–5 days after admission to hospital[19,27,44], which is similar to our findings. It has been postulated that anaemia, capillary stasis and hypoxia could initiate AP in falciparum malaria[27,4], and these mechanisms may be involved in babesial AP as well.

The pancreas is highly sensitive to ischaemia and perfusion disturbances[34,45,57], and there are several potential mechanisms whereby canine babesiosis may result in pancreatic ischaemia. Firstly, haemolytic anaemia plays a central role in babesiosis, with the occurrence of both intravascular and extravascular haemolysis[32]. Anaemia may lead to tissue-level hypoxia and anaerobic tissue metabolism[31,32,51], which may give rise to multiple organ failure, due especially to the generation of potent oxidising substances[31]. Thus, anaemic hypoxia may in part explain the development of AP in the anaemic dogs in our study, but it does not account for its development in the non-anaemic dogs.

Secondly, organ dysfunctions in acute haemolytic disease may be further promoted by the local vasoconstricting effects of haemolysate. This vasoconstriction may be as a result of binding of free haemoglobin to nitric oxide, and the acceleration of free oxygen radical formation by haemoglobin breakdown products[13]. The development of AP as a sequel to acute haemolytic disease has been described in humans[6,13,56], and free haemoglobin and/or its breakdown products may thus offer a further mechanism for AP development in some of our cases. However, such development of AP in humans usually only occurs in cases with massive intravascular haemolysis, rather than in milder haemolytic states[13]. Haemolysis of this magnitude is unlikely in most cases of canine babesiosis, and it is therefore, at most, a contributor to, rather than the cause of, pancreatitis.

A third potential mechanism for the development of pancreatic ischaemia in babesiosis is hypotensive shock. Shock results in splanchnic organ ischaemia secondary to disproportionate perfusion alterations[39]. The development of AP is thus a potential complication following a hypotensive state with splanchnic

hypoperfusion[34], which may lead to pancreatic lysosomal disruption in-vitro[11]. It has been suggested that babesial shock, like endotoxaemic shock, passes through a hyperdynamic phase followed by hypotensive shock[25], and hypotension has recently been shown to be common in babesiosis[26]. Pancreatic necrosis caused by ischaemia may produce fewer clinical signs than other forms of pancreatitis, at least in the initial stages of the disease[57]. This could account for the delay in diagnosis of AP in our study (median 2.5 days post-admission), since the clinical signs observed were often initially attributed solely to babesiosis.

Pancreatic ischaemia, brought about by 1 or more of the above-mentioned mechanisms, may in itself lead to the development of AP[20,34,39,57,59]. However, reperfusion injury (following rehydration, correction of hypotension, or correction of anaemia by blood transfusion) of an ischaemic, inflamed pancreas can lead to the conversion of hypoxanthine to xanthine and oxygen free radicals[50]. Oxygen free radicals, known to be essential to the development of all forms of pancreatitis, initiate inflammatory cell chemotaxis and infiltration, and alter zymogen granule membranes[50]. Acute pancreatitis has been experimentally induced by ischaemia and reperfusion injury[17,49], with the degree of apoptotic acinar cell death and neutrophil infiltration of the gland reaching a maximum at 48 hours after reperfusion[17]. The median time of AP diagnosis in our study was 2.5 days post-admission, which raises the possibility that ischaemia-reperfusion injury could be primarily involved in its pathogenesis. Lending further support to this hypothesis is the fact that only 3 dogs had a haematocrit less than 0.20 ℓ/ℓ at the time of AP diagnosis, and anaemia alone, without the effects of reperfusion, is unlikely to be the sole pathophysiological mechanism involved.

Pancreatic pathology, once initiated, may potentially be perpetuated by a systemic inflammatory process, such as occurs in babesiosis. Little evidence exists that inflammatory cytokines themselves can initiate AP[38], but their pro-inflammatory roles in the regulation of the severity of pancreatitis is well established[38,43]. For example, acinar cell expression of cholecystokinin receptors is induced by inflammatory cytokines[38]. Tumour necrosis factor-α has been shown to stimulate apoptosis in pancreatic acini of rats, and its neutralisation was associated with greatly inhibited apoptosis[18]. It is therefore possible that the severity of AP in babesiosis may be exacerbated, if not primarily initiated, by inflammatory cytokines, given the postulated cytokine milieu (including pro-inflammatory cytokines) of complicated canine babesiosis.

Additional potential factors in the pathogenesis of babesial AP may include IMHA, haemoconcentration, altered lipid metabolism, and DIC.

Immune-mediated mechanisms have been implicated as initiating events of AP[50,57]. Up to 5 % of naturally occurring canine AP cases have been associated with autoimmune diseases, including IMHA[11], and this association between IMHA and AP has also been recognised in humans[13]. Immune-mediated haemolytic anaemia was present in 6 dogs in this study, and may be a contributing factor in the development of babesial AP.

Haemoconcentration with an admission haematocrit 0.47 ℓ/ℓ has also been identified as an early risk factor for necrotising pancreatitis in humans with AP[2]. This was seen in 1 of our 2 haemoconcentrated cases (Dog 1), in which pancreatic necrosis was confirmed histologically.

Four of the dogs had lipaemic sera, which may have been the consequence of AP, since pancreatitis has historically been considered a cause of hyperlipidaemia[20]. However, this cause-and-effect relationship has recently been challenged[22], and it is known that hyperlipidaemia[20] and hypertriglyceridaemia[22] may constitute risk factors for the development of canine AP. This raises the question whether altered lipid metabolism in babesiosis may potentially be an initiating event of AP. Altered lipid metabolism has not yet been demonstrated in *B. canis* infection, but such alterations have been documented in human malaria[29]. Post-prandial lipaemia was unlikely in these cases, since all 4 dogs were anorexic at the time of sampling.

Disseminated intravascular coagulation has been documented in canine babesiosis[36], and since thromboembolism has been implicated in the pathogenesis of AP[45,57], DIC may have been responsible for the development of AP in Dog 1, in which thrombosis of intra-pancreatic bloodvessels was demonstrated histologically. However, a study of fatal canine AP identified 6 % of cases with laboratory data compatible with DIC[23], and the pancreatic thrombosis observed in this case may therefore have been the result, rather than the cause, of pancreatitis.

A human suffering from chronic pancreatitis has been documented to have relapsed into AP whilst suffering from babesiosis[15]. Two dogs (Dogs 4 and 12) in this study also had a history of suspected chronic pancreatitis, which may have served as a risk factor for the development of babesial AP.

A cause-and-effect relationship between glucocorticoid therapy and AP is especially controversial, with no firm experimental evidence in dogs to support the clinical suspicion[49,50]. Pancreatitis has, however, been described in dogs following high-dose corticosteroid treatment for a week or longer[11,20]. In the present study, corticosteroids had been administered to 8 dogs before the development of AP. The duration of such treatment before AP diagnosis was, however, less than that reported to initiate AP in dogs[20], and corticosteroids are therefore unlikely to be a significant contributing factor to pancreatitis in our study.

The 26 % mortality rate in this study (4 dogs died naturally and 1 was euthanased) is comparable to the reported mortality in AP due to other causes, which may be as high as 27 %[42] to 40 %[11,40]. Poor prognostic signs in AP include respiratory distress, acute renal failure, and neurological abnormalities[59]. This was also seen in our patients, since 4 of the 5 dogs (80 %) that died shared at least 1 of these complications.

The histologic pancreatic lesions in 4 necropsied dogs were consistent with a diagnosis of acute pancreatitis, as defined in human disease[5]. It may also be classified as acute pancreatic necrosis, since this term has been used in the veterinary literature to emphasise the basic necrotic lesion in the interstitial and peripancreatic adipose tissue, rather than in the pancreatic parenchyma[28]. It is noteworthy that the pancreatic lesions in these 4 dogs were often interspersed with sections of unaffected, histologically normal gland. This necessitates the evaluation of multiple histologic sections in order not to overlook more localised pathology, such as has also been described for AP secondary to other causes[28].

The so-called 'gut' or 'digestive form' of babesiosis, characterised by gastrointestinal disturbances, has generally been considered a rare complication of the disease[25,32,33]. A critical re-appraisal of this complication may be in order considering the new data brought to light by this study, since this syndrome may in fact represent AP. Pancreatic inflammation may extend to the adjacent stomach, duodenum, ascending and transverse colon[20,23], accounting for the gastrointestinal clinical signs seen in AP. Gastrointestinal abnormalities reported as a complication of canine babesiosis have included vomition[1,3,12,24,33,36], diarrhoea[1,12,36], abdominal pain[12,24,33,36], enteritis[3], and enterorrhagia[30]. Owing to a low index of suspicion, investigation for AP was not undertaken in these reports. Gross patho-

logical findings were, however, reported in 1 study[36], in which 2 dogs had pancreatic oedema, petechiation and ecchymoses.

The development of AP as a sequel to canine babesiosis influences the treatment regimens of the affected dogs, incurs additional treatment costs, results in prolonged periods in hospital, and worsens patient prognosis. Delayed diagnosis and treatment of AP may lead to increased mortality in cases where anorexia, vomiting, and signs of abdominal pain are initially attributed to another cause[11]. Early identification of these symptoms in a dog with babesiosis should increase the clinician's index of suspicion for potential AP, resulting in timeous diagnostic investigations and therapeutic intervention.

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Book review — Boekresensie

Nematode parasites of vertebrates (2nd edition)**: their development and transmission**

R C Anderson

2000. CABI Publishing, Wallingford, 672 pp., hard cover. US$ 185. ISBN 0 85199 421 0.

The 1st edition of this book appeared in 1992, and summarised and synthesised the knowledge of the basic features of the development and transmission of the parasitic nematodes of vertebrates. This 2nd edition has kept the original aim in focus, which is to continue to place this information in the context of the modern classification as found in the Commonwealth Institute of Helminthology (CIH) keys to the nematode parasites of vertebrates. This book will be of practical use to parasitologists, physicians, veterinarians, zoologists, and wildlife and fisheries biologists.

There are few books available in English that so completely address the development and transmission of parasitic nematodes. There are several significant improvements to this edition. Firstly, 45 references have been added, and the number of nematode species increased by 34, giving an overall total of 595. Secondly, the illustrations that have been redrawn improve the quality throughout. Thirdly, the inclusion of information on free-living stages will be useful to the field researcher, and one example is the 3rd-stage larvae of the ascaridoids.

Three aspects make this book user-friendly. One is that of the format of the 'Contents' at the beginning of the book, which is similar to that of the previous edition, where orders are followed by superfamilies and reference lists. Secondly, a list of figures follows the contents, giving the reader an easy guide for reference. Lastly, the index, which comprises 15 pages, is accurate. One discrepancy was noted, however: *Streptocara* is listed to appear on page 415 but in fact appears on page 451.

This well-written and well-indexed reference book on a diverse biological group is highly recommended for any parasitology library. The cost is US$185 and is a worthwhile investment because of the quality text it offers and its uniqueness of content.

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