Hypoglycaemia in virulent canine babesiosis:

Prevalence and risk factors

by

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The task Thy wisdom hath assigned
O let me cheerfully fulfil; in all my
Works
Thy presence find,
And prove Thy acceptable will.

Thee may I set at my right hand
Whose eyes my inmost substance see;
And labour on at Thy command,
And offer all my works to Thee.

Charles Wesley

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SU MMARY

A study was conducted to determine the prevalence of and potential risk factors for hypoglycaemia in canine babesiosis due to *Babesia canis rossi*. Plasma glucose concentration was measured at presentation in 250 dogs with babesiosis, of which 111 were admitted to hospital.

The overall prevalence of hypoglycaemia (< 3.3 mmol/l) was 9% (23/250). Twenty-two hypoglycaemic dogs required admission, making the prevalence of hypoglycaemia in admitted cases 19.8%. Sixteen dogs had severe hypoglycaemia (≤ 2.2 mmol/l) of which 5 had a blood glucose < 1 mmol/l. Hyperglycaemia (> 5.6 mmol/l) was present in 38 (38/250; 5.2%) dogs of which 21 (21/250; 8.4%) were admitted and severe hyperglycaemia (> 15 mmol/l) did not occur.

Risk factors for hypoglycaemia identified by univariable analysis were: Collapsed state ($P < 0.00001$), severe anaemia ($P = 0.0002$), icterus ($P = 0.003$), age below 6 months ($P = 0.02$) and vomition ($P = 0.03$). After logistic regression analysis, collapsed state (OR = 17.8, 95% CI: 1.9 to 171, $P = 0.01$) and young age (OR = 2.8, 95% CI: 0.8 to 9.7, $P = 0.1$) remained significantly associated with hypoglycaemia. Toy breeds and pregnant bitches were not at higher risk for hypoglycaemia than other dogs. Hypoglycaemia was only associated with overt neurological signs in two dogs.

Blood glucose concentration should ideally be measured in all dogs requiring treatment for babesiosis, but is mandatory in collapsed dogs, puppies and dogs with severe anaemia, vomition or icterus. Many cases have probably been misdiagnosed, as

cerebral babesiosis in the past and hypoglycaemia should be suspected in any case with coma or other neurological signs; however, this should in no circumstances be the only reason to suspect hypoglycaemia.

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LIST OF ABBREVIATIONS

mmol/l	millimoles per litre
G-6-P	glucose-6-phosphatase
Glu	glucose
%	percent
ºC	degrees Celsius
TSP	total serum protein
ISA	in saline agglutination
nm	nanometre
ml	millilitre
ADP	adenosine diphosphate
ATP	adenosine triphosphate
H_2O	water
CO_2	carbon dioxide
SIRS	systemic inflammatory response syndrome
MODS	multiple organ dysfunction syndrome
NaF/Ox	sodium fluoride oxalate
NADP	nicotinamide adenine dinucleotide phosphate
SD	standard deviation
n	number
OR	odds ratio
KCl	potassium chloride
kg	kilogram
ICU	Intensive Care Unit

CHAPTER 1 LITERATURE REVIEW

1.1 CANINE BABESIOSIS

Canine babesiosis in South Africa is a tick-borne disease caused by the haemoprotozoan parasite *Babesia canis rossi*.[1] Different subspecies of the parasite occur worldwide and are associated with varying pathogenicity. There are three subspecies of *B. canis*: *Babesia canis canis* (Europe), *Babesia canis vogeli* (Northern Africa and North America) and *Babesia canis rossi* (Southern Africa).[1] *B. canis rossi* is transmitted by *Haemophysalis leachi* and is highly pathogenic.[2, 3, 4] Babesiosis is a common cause of morbidity and mortality of dogs in South Africa, accounting for 12% of cases presented at the Onderstepoort Veterinary Academic Hospital (OVAH) and for approximately 12% of canine mortalities seen by private veterinarians in South Africa.[5, 6]

Babesiosis can range from a very mild to a peracutely fatal disease.[2] The parasite primarily affects the erythrocytes, with haemolytic anaemia being a hallmark of the disease,[7] but multiple organ involvement also occurs.[8]

Canine babesiosis can be clinically classified as uncomplicated or complicated.[9] Uncomplicated babesiosis is divided into mild, moderate and severe, according to the severity of the anaemia. Complicated babesiosis involves clinical signs that are

unrelated to the haemolytic disease and involves organs and systems other than the haematological system.[7, 8, 9] Organs that can be involved are the kidney, lungs, brain and liver. Recently it has been proposed that an inflammatory response, rather than the parasite itself, is the cause of the variety of complications and therefore the inflammatory response syndrome with progression to the multiple organ dysfunction syndrome, may underlie the complicated forms.[8, 9, 10]

1.2 CARBOHYDRATE METABOLISM

Maintenance of normal blood glucose levels (euglycaemia) is dependent upon the balance of glucose entering and leaving the blood. Euglycaemia represents a dynamic balance between supply, storage, release and consumption of glucose. Glucose is supplied by intestinal absorption of dietary glucose or by hepatic glucose production from its precursors, i.e., carbohydrates (fructose and galactose) and amino acids, a process known as gluconeogenesis.[11] Glucose that is absorbed from the gut is circulated to all tissues where it is oxidized, used to produce energy or stored. The liver has central importance in carbohydrate metabolism. Hepatic carbohydrate metabolism includes the storage of glucose as glycogen (glycogenesis), release of glucose from glycogen stores (glycogenolysis), gluconeogenesis and the metabolic conversion of non-glucose hexoses to glucose. [11, 12]

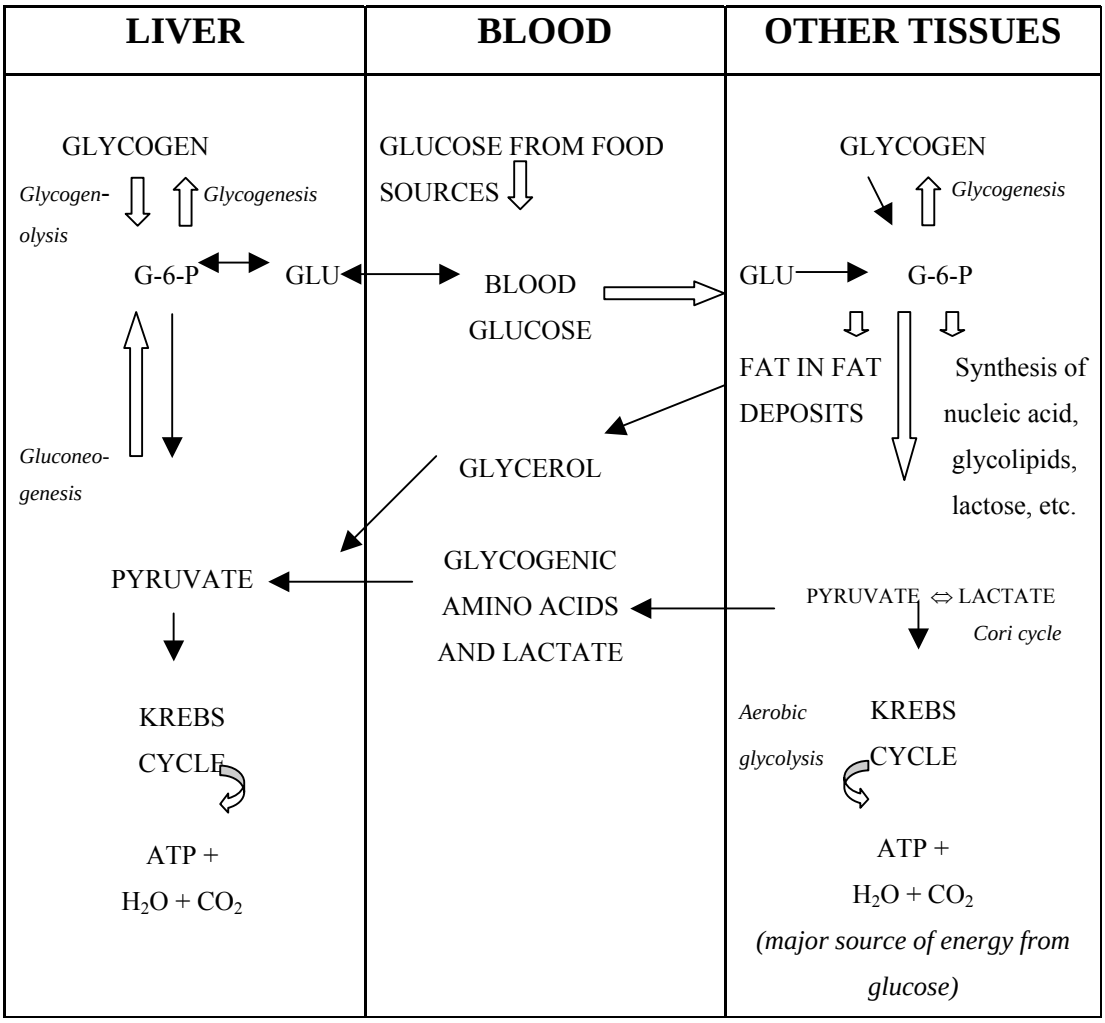
The absorptive process varies with the degree of systemic metabolism. All conditions affecting gastrointestinal digestive processes substantially affect glucose absorption. In the post-absorptive state, hepatic production is the major source of supply for maintaining blood glucose.[13]

Low blood glucose stimulates glucose-6-phosphatase activity, which initiates glycogenolysis. Because the brain's daily requirement of glucose exceeds the amount of glucose stored in the liver as glycogen, gluconeogenesis is necessary.[14] Gluconeogenesis from amino acids is the most important source of glucose when carbohydrate intake is low and glycogen stores are depleted.

The liver has a great metabolic reserve for maintaining euglycaemia. Less than 30% of functional hepatic mass is necessary to maintain glucose concentrations in the blood.[14]

Glucose metabolism is summarised in Figure 1.

Figure 1: Glucose metabolism: [12]



1.3 HYPOGLYCAEMIA IN SEVERE INJURY AND INFECTION

Patients with sepsis, trauma or severe debilitating disease commonly enter a hypermetabolic stress state that alters carbohydrate metabolism.[15] This is the systemic response to severe injury or infection. It manifests as a syndrome (systemic inflammatory response syndrome – SIRS) consisting of hypermetabolism, a hyperdynamic cardiovascular state and clinical manifestations of fever or hypothermia,

tachycardia, tachypnoea and/or leukocytosis.[16] A physiologic hyperdynamic state usually accompanies the hypermetabolism.[17] The primary hallmark is a fall in systemic resistance with an associated rise in cardiac output. SIRS can ultimately lead to multiple organ dysfunction syndrome (MODS).

Severe injury or infection is associated with enhanced cellular uptake of glucose.[18, 19] During the inflammatory response alterations in glucose and fat metabolism occur. Gluconeogenesis increases, as does the rate of lactate and pyruvate formation. Glucose recycling from lactate and alanine accounts for most of the increase in glucose production during stress. Although stress is typically associated with increased gluconeogenesis there is evidence that septic stress is distinguished by a biphasic response; lethal models of sepsis in animals demonstrate an initial phase of hyperglycaemia during which gluconeogenesis is increased, followed by a subsequent phase during which glucose production is suppressed and hypoglycaemia occurs.[15]

Hepatic glycogenolysis is the primary source of glucose during short periods of fasting. After 24 hours of fasting, hepatic glycogen stores are depleted and gluconeogenesis then plays a greater role in the maintenance of euglycaemia.[13, 20]

Hypoglycaemia is a well-documented complication of severe bacterial infections in humans. Infections impair gluconeogenesis and glycogen depletion occurs.[21] Hypoglycaemia may occur as a result of increased insulin-dependent utilization of glucose (pancreatic β-cell tumour and insulin overdose), decreased production of

glucose (severe hepatic disease and hypoadrenocorticism), or a combination of increased utilization and decreased production of glucose (e.g. sepsis).[13]

1.4 HYPOGLYCAEMIA IN DOGS

Hypoglycaemia in dogs is a well-described finding. Several reports of mild to severe hypoglycaemia have been published in dogs with critical illness,[22, 23] endotoxic shock,[24] sepsis,[25, 26] parvoviral enteritis[27, 28, 29] and non-specific severe diarrhoea,[28] as well as in endocrinopathies, particularly insulinoma.[22] Alterations in blood glucose represent one of the most consistent findings in canine sepsis.[22, 23, 30] A direct relationship between blood glucose concentrations and survival in critically ill dogs has been reported.[25, 31, 32]

Causes of canine hypoglycaemia are listed below[33, 34]:

Glucose Overutilization and Increased losses:

1. Hyperinsulinism
    a. Therapeutic overdose
    b. Functional β-cell tumour
2. Extra-pancreatic neoplasm
3. Cachexia with fat depletion
4. Sepsis
5. Hunting dog hypoglycaemia
6. Renal glycosuria

Glucose Underproduction:

1. Neonatal hypoglycaemia
2. Transient juvenile hypoglycaemia
3. Hypoadrenocorticism
4. Drugs
    a. Alcohol
    b. Propranolol
5. Substrate deficiency
    a. Starvation
    b. Malabsorption
6. Liver disease
    a. Severe hepatitis
    b. Cirrhosis
    c. Portosystemic shunts
7. Enzyme deficiencies
    a. Type I glycogen storage disease (Von Gierke's disease)
    b. Type III glycogen storage disease (Cori's disease)

1.5 HYPOGLYCAEMIA IN BABESIOSIS

Hypoglycaemia is a relatively new finding in babesiosis, but early work pointed to its likely occurrence. Hepatic glycogen was depleted in pups[35] and calves[36] that died of the disease, while glucose dropped significantly in calves with *B. bovis* even though it did

not reach subnormal concentrations.[36] Hypoglycaemia occurred in 36.7% of dogs infected with *Babesia* and *Ehrlichia* spp, and *Hepatozoon canis.*[37]

Schetters injected 5 dogs with *Babesia canis* antigens and none of them developed hypoglycaemia.[38] In contrast, hypoglycaemia was found to occur in 5 dogs, in a study where blood glucose levels were measured in 30 dogs with naturally occurring babesiosis.[39] It was noted in this particular study that there were striking differences between the hypoglycaemic dogs and the normoglycaemic dogs. The hypoglycaemic dogs had a lower haematocrit, higher lactate and a high mortality rate.[39]

1.6 HYPOGLYCAEMIA IN MALARIA

The similarities between babesiosis and malaria have long been noted. Both diseases are characterised by anaemia and share very similar complications.[10] Therefore malaria research can provide a base for research in canine babesiosis.[3, 10]

Hypoglycaemia in malaria is a well-described finding[21, 40, 41, 42] and was documented in severe malaria infections as early as 1944[43]. Several contributing factors have been implicated, and include increased peripheral requirement for glucose during febrile and critical illness;[10, 15, 44] obligatory demands of the parasites that use glucose as their major fuel;[45] hyperinsulinaemia (often attributed to quinine);[46, 47] failure of hepatic gluconeogenesis and glycogenolysis[48, 49] and increased glucose consumption by anaerobic glycolysis due to tissue hypoxia.

Hypoglycaemia is a serious and common complication of *Plasmodium falciparum* malaria, particularly in children[40] and pregnant women,[50] and is associated with a poor prognosis.[42, 51, 52, 53] Response to treatment is variable and intravenous dextrose does not reliably improve glycaemic status or survival.[40, 41, 53, 54]

1.7 POTENTIAL RISK FACTORS FOR HYPOGLYCAEMIA IN BABESIOSIS

It would be of substantial benefit to the clinician to know whether certain dogs with babesiosis are at greater risk for hypoglycaemia than others. The signalment alone may help to ascertain which patients are at risk. Neonatal patients often present with hypoglycaemia due to poor glucose regulation.[13] Young, small breed dogs have a higher incidence of hypoglycaemia especially during stress and hunting dogs may develop hypoglycaemia due to exercise.[13] One study showed that 57% of young dogs with haemorrhagic gastroenteritis had hypoglycaemia[55], while another study had a prevalence of 3%.[27]

Certain animals may be at higher risk for presenting with hypoglycaemia.

- Various reports show that **severe debilitating disease** and endotoxic shock can lead to hypoglycaemia in dogs.[24, 25, 26]

- Some studies have shown that **puppies** have lower blood glucose levels than adults.[56, 57] Hypoglycaemia in puppies (less than six months of age) is a well-documented condition, with an increased incidence seen in the toy breeds.[33, 58]

- **Toy breeds** (Poodles, Yorkshire Terriers, Chihuahuas) are more prone to hypoglycaemia, especially during periods of stress or fasting.[33, 59, 60]

- Hepatic glycogenolysis is the primary source of glucose during short periods of **fasting**.[13, 20] The liver has a great metabolic reserve for maintaining euglycaemia. Less than 30% of **functional hepatic mass** is necessary to maintain glucose concentrations in the blood.[14]

- Previous studies have shown that some dogs with severe **diarrhoea** and also dogs with canine parvoviral enteritis have hypoglycaemia.[27, 28, 29] All conditions affecting gastrointestinal digestive processes substantially affect glucose absorption. This includes **vomiting**.

- Hypoglycaemia can also occur in **pregnant** and lactating bitches, usually during late pregnancy and early post-partum.[33, 61]

- **Neurological signs** in dogs with babesiosis have always been used as a pathognomonic sign for cerebral babesiosis. Other causes, notably hypoglycaemia was previously not considered.

1.8 PREVALENCE

Prevalence refers to the number of cases as a proportion of the population at risk at a specified point in time.[62] A prevalence study is similar to a cross-sectional study. A prevalence study provides information about the magnitude of a problem and not the cause or effect.

1.9 NORMAL VALUES FOR GLUCOSE

The published normal range for blood glucose in the dog is 3.3 - 5.6 mmol/l.[13, 63] Hypoglycaemia for this study was therefore defined as a blood glucose concentration less than 3.3 mmol/l.

1.10 DETERMINATION OF GLUCOSE

The glucose concentration of routinely stored blood decreases due to metabolism via glycolysis. This problem is worsened by inflammatory states due to high metabolic activity of, and glucose consumption by, leukocytes.[64] Spurious hypoglycaemia due to improper sample handing was reported in canine heptozoonosis.[64]

Regardless of which analytic procedure is used, a correct result will not be obtained unless precautions are taken to prevent a significant change in the glucose

concentration.[65] Sodium fluoride oxalate (NaF/Ox) prevents coagulation and inhibits blood cell glycolysis.[65, 66] In sterile blood samples taken in NaF/Ox, glucose is stable for up to ten days at room temperature.[65] Glucose was stable after NaF/Ox blood was centrifuged for ten minutes and stored at -20°C for 30 days before analysis.[67]

In this study the glucose was measured using the hexokinase method. The enzyme hexokinase catalyses the reaction of glucose with adenosine triphosphate (ATP) to form glucose-6-phosphate and adenosine diphosphate (ADP). A second enzyme, glucose-6-phosphate dehydrogenase (G6PDH), catalyses the reaction of the glucose-6-phosphate produced with nicotinamide adenine dinucleotide phosphate (NADP) to form 6-phosphogluconate and reduced NADPH. Since NADPH absorbs strongly at 340 nm, the increased absorption at this wavelength is used as a measure of the initial glucose concentration.[65]

The reference hexokinase method minimizes interference by protein and other serum constituents.[66]

CHAPTER 2 STUDY OBJECTIVES

2.1 PROBLEM STATEMENT

Hypoglycaemia is likely to be a significant problem in severe canine babesiosis. No studies have been conducted to determine the prevalence of hypoglycaemia, despite the possibility that it may be a life-threatening complication and an important prognostic indicator. Risk factors for hypoglycaemia in babesiosis are currently unknown.

2.2 OBJECTIVE OF THIS STUDY

To determine the prevalence of and potential risk factors for hypoglycaemia in canine babesiosis.

2.3 RESEARCH QUESTIONS

1. What is the prevalence of hypoglycaemia in canine babesiosis?

2. What are the potential risk factors for hypoglycaemia?

2.4 BENEFITS

1. This study provides important information about hypoglycaemia in dogs with babesiosis caused by *Babesia canis rossi*. The results have important therapeutic and prognostic implications.

2. This project is in partial fulfilment of the requirements of the MMedVet (Med) degree.

CHAPTER 3 MATERIALS AND METHODS

3.1 MODEL SYSTEM

Two-hundred-and-fifty client-owned dogs with clinical babesiosis, presented sequentially at the Onderstepoort Veterinary Academic Hospital over a three month period, were prospectively included in the study. Babesiosis was diagnosed by the presence of parasites on a thin stained[a] capillary blood smear in association with typical clinical signs. Owners signed a consent form for their animals to take part in the study (Addendum A).

The attending clinician (not one of the investigators) at the Outpatients clinic decided whether or not the dog should be admitted to the Intensive Care Unit without prior knowledge of the blood glucose levels, thereby avoiding bias.

3.2 OBSERVATIONS

Signalment, history and clinical data

The primary investigator, a veterinarian conducting a parallel study using the same patients or a veterinary nurse contracted for the study, collected all the data. Breeds

[a] Rapidiff stain (C A Milsch, PO Box 943, Krugersdorp, 1730, South Africa)

were classified as toy, small and medium, large and giant according to the Kennel Union of South African guidelines (Addendum B). Owners completed a questionnaire about the time since last full meal, vomiting, diarrhoea and pregnancy status (Addendum C).

The presenting microhaematocrit was recorded. The data collector performed a full clinical examination and noted the presence or absence of clinical icterus (yellow mucous membranes), neurological signs (e.g. coma, ataxia, seizures) and also documented the dog's habitus (collapsed, depressed or alert).

Patient records

Patient records were photocopied and filed according to the research number.

Microhaematocrit

A heparinised 1ml syringe is routinely used to determine the haematocrit, total serum protein (TSP) and in-saline agglutination (ISA) status at presentation on all canine babesiosis cases. The haematocrit was determined using a non-heparinised microhaematocrit tube[b]. The sample was centrifuged for five minutes using a microhaematocrit centrifuge[c]. The packed cell proportion was determined using a Hawksley haematocrit reader[d].

[b] Marienfeld Laboratory Glassware, Germany
[c] Jouan Hema-C microhaematocrit centrifuge, Hawksley and Sons, Ltd., Sussex, United Kingdom
[d] Hawksley and Sons, Ltd, Sussex, United Kingdom

Serum glucose determination

Blood was collected prior to treatment from all dogs, using the cephalic or jugular vein, into an evacuated glass tube containing sodium fluoride potassium oxalate (NaF/Ox)[e]. Samples were centrifuged[f] (1730 x g) for ten minutes and the plasma separated and stored at 4°C. Where possible, plasma glucose was measured within 15 minutes. These results were only made available after the attending clinician had decided whether or not the dog should be admitted, thereby avoiding bias. Where necessary, samples were stored at 4°C for up to three days. Glucose is stable under these conditions.[65] Glucose was measured using the hexokinase method[g].[65, 66]

3.3 SAMPLE SIZE

The sample size of 250 was determined with the assistance of a veterinary epidemiologist, using PASS[h] on a personal computer. Calculations were based on an expected prevalence of 6% in dogs with babesiosis[39], with a confidence level of 95% and an absolute error of 3%.

[e] Vacutainer System (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth. UK)
[f] Jouan. Benchtop centrifuge B3.10, Winchester, Virginia, USA
[g] Technicon RA 1000 system (Miles Inc. Diagnostics Division, Tarrytown, New York. USA
[h] Hintze, J. (2003) NCSS and PASS. Kaysville, Utah.

3.4 DATA ANALYSIS

Data was entered on an Excel® spreadsheet (Microsoft Corporation). A veterinary epidemiologist[i] performed the statistical analysis.

The published reference range for blood glucose in the dog is 3.3 - 5.6 mmol/l.[13, 63] Hypoglycaemia in this study was defined as a blood glucose concentration less than 3.3 mmol/l[12, 13, 63] and hyperglycaemia as above 5.6 mmol/l. Glucose concentrations ≤ 2.2 mmol/l were classified as severe hypoglycaemia.[33, 68]

Age, haematocrit, breed, sex, pregnancy status, mental status, time since last meal, history of vomiting or diarrhoea, neurological signs and icterus were assessed for their usefulness as predictors of hypoglycaemia. Patients were classified into discrete, clinically meaningful categories of each predictor variable. Descriptive statistics included the mean and median blood glucose concentrations for each category of each predictor variable. The medians for each category of a variable were compared using Kruskal-Wallis one-way ANOVA on ranks. The prevalence of hypoglycaemia, with 95% confidence intervals, was calculated for admitted and non-admitted cases.

Univariable analysis of each predictor variable was performed for the binary outcome (hypoglycaemia) using contingency tables and Fisher's exact test. Variables with $P < 0.3$ on univariable analysis were selected for testing in a multivariable logistic

[i] Thompson, N.P. Department of Production Animal Studies, Section of Epidemiology, Faculty of Veterinary Science, Onderstepoort, Pretoria, South Africa.

regression model, which was then developed by backward elimination. Variables remained in the model if they (or, in the case of polytomous predictor variables, at least one of their design variables) were significant in the model (Wald $P < 0.1$) or if their removal resulted in >10% change in the effect of other variables. Statistical analysis was done on a personal computer using NCSS.[j]

[j] Hintze, J. (2003). NCSS and PASS. Kaysville, Utah.

CHAPTER 4 RESULTS

A complete data set is provided in Addendum E.

4.1 PREVALENCE

Almost half (111/250; 44.4%) of the dogs in the study were considered to be severely ill by the attending clinician and were admitted to the Intensive Care Unit. Twenty-three of the 250 dogs (9.8%) were hypoglycaemic at presentation (Table 1). Twenty-two (95.7%) of the hypoglycaemic dogs were admitted. The 23rd hypoglycaemic dog (blood glucose = 3.2mmol/l) was still alert and it was not deemed necessary to admit the dog. The attending clinician did not know the blood glucose level of the dog. The prevalence of hypoglycaemia in admitted cases was 19.8%, compared with 0.72% in non-admitted cases. There was a significant difference in prevalence of hypoglycaemia between admitted and non-admitted cases ($P < 0.00001$).

Sixteen dogs (69.6% of hypoglycaemic dogs; 14.4% of all admitted cases) had severe hypoglycaemia (≤ 2.2 mmol/l). Five of these (21.7% of hypoglycaemic dogs; 4.5% of admitted cases) had blood glucose concentrations below 1.0 mmol/l.

Table 1. Prevalence of hypoglycaemia (blood glucose < 3.3 mmol/l) in dogs with babesiosis.

	n	Prevalence (%)	95% confidence interval
Admitted cases	22/111	19.8 [a]	13.1 to 28.7
Non-admitted cases	1/139	0.72 [b]	0.04 to 4.54
TOTAL	23/250	9.20	6.05 to 13.7

[a,b] Prevalence differs significantly between groups (Fisher's exact test, $P < 0.00001$)

Fifteen percent of the dogs (38/250) presented with hyperglycaemia (see Addendum E). Fifty-five percent of hyperglycaemic cases (21/38) were ill enough to warrant admission, thus making up roughly the same proportion as hypoglycaemic cases in the admitted group (21/111; 18.9%). The highest blood glucose level measured in this study was 10.3 mmol/l.

Descriptive statistics are provided in Table 2. Data are incomplete where owners did not know all the answers to the questionnaire. The blood glucose concentrations in the 250 dogs ranged from 0.1 – 10.3 mmol/l.

There were significant differences in plasma glucose concentration between predictor levels (Table 2). There was a statistically significant difference between dogs that were clinically collapsed and the alert and depressed groups. Young dogs also appeared more at risk than older dogs. A statistical difference was also found in dogs with a low haematocrit. Dogs with hypoglycaemia and those without did not differ statistically for time since last meal, vomition and neurological signs. There was no statistical

significant difference between toy breed dogs and medium or large breed dogs. All 9 pregnant dogs had blood glucose concentrations within the normal range. Dogs that were anorexic for more than 4 days were not at higher risk for developing hypoglycaemia while suffering from canine babesiosis.

While there were statistically significant differences for age, haematocrit and habitus, the scatter of the data was such that there was an overlap between the groups. This is evident from the medians and ranges provided.

Table 2. Plasma glucose concentration and putative risk factors in canine babesiosis.*

Variable	Category	n	Blood glucose concentration (mmol/l)	
			Median	Range
Age	<6 months	49	4.5 [ab]	0.1 – 7.3
	6-11 months	47	4.9 [a]	2.2 – 6.2
	≥12 months	154	4.5 [b]	0.7 – 10.3
Haematocrit	<10	43	4.5 [ab]	0.3 – 7.0
	10-19	125	4.8 [a]	0.1 – 10.3
	20-39	65	4.5 [a]	2.0 – 6.0
	≥40	15	3.8 [b]	2.5 – 6.9
Breed	Small	28	4.5 [a]	1.8 – 7.3
	Medium	88	4.5 [a]	0.1 – 9.5
	Large	134	4.8 [a]	0.3 – 10.3
Sex	Male	131	4.6 [a]	0.3 – 10.3
	Female	119	4.5 [a]	0.1 – 7.0
Pregnancy status	Non-pregnant	110	4.5 [a]	0.1 – 7.0
	Pregnant	9	4.8 [a]	3.4 – 6.9
Habitus	Alert	80	4.6 [ab]	3.2 – 7.3
	Depressed	118	4.7[a]	1.7 – 9.5
	Collapsed	52	4.1 [b]	0.1 – 10.3
Time since last meal	<1 day	135	4.6 [a]	0.1 – 9.5
	1-3 days	87	4.6 [a]	0.5 – 10.3
	≥4 days	26	4.7 [a]	1.9 – 9.8
Vomiting	Absent	212	4.6 [a]	0.1 – 9.8
	Present	35	4.3 [a]	0.5 – 10.3
Diarrhoea	Absent	217	4.6 [a]	0.1 – 9.8
	Present	30	4.6 [a]	2.0 – 10.3
Neurological Signs	Absent	242	4.6 [a]	0.1 – 10.3
	Present	8	4.1 [a]	0.3 – 6.9
Icterus	Absent	218	4.6 [a]	0.1 – 7.3
	Present	31	4.4 [a]	1.1 – 10.3
Admission	Not admitted	139	4.6 [a]	3.2 – 7.3
	Admitted	111	4.5 [a]	0.1 – 10.3
TOTAL		250	4.6	0.1 – 10.3

* Some data are missing where owners did not know all the answers to the questionnaire.
[a,b] Medians for categories of a variable, with different superscripts, differ significantly ($P<0.05$, Kruskal-Wallis one-way ANOVA on ranks)

4.2 RISK FACTORS

The variables with $P < 0.3$ on univariable analysis were age, haematocrit, mental status, vomiting, neurological signs and icterus (Table 3). These variables were tested in a multivariable logistic regression model. Although some of them had high odds ratios the only predictor variables statistically significant in the model were habitus ($P = 0.01$) and age ($P = 0.11$) Age was included, because its removal would have resulted in >10% change in the effect of other variables (Table 4).

Collapsed dogs were 17.8 times more likely to be hypoglycaemic than alert dogs, and dogs younger than 6 months of age were 2.8 times more likely to be hypoglycaemic than dogs older than one year of age. The other variables remained in the model as confounders (Table 4).

Table 3. Potential risk factors for hypoglycaemia in canine babesiosis: univariable screening.

Variable	Category	Hypoglycaemia		OR *	95% confidence interval	*P* §
		present	absent			
Age	<6 months	10	39	3.03	1.22 to 7.55	0.02
	6-11 months	1	46	0.26	0.03 to 2.03	0.31
	≥12 months	12	142	1 †		
Haematocrit	<10	12	31	12.2	2.57 to 57.9	0.0002
	10-19	8	117	2.15	0.44 to 10.5	0.50
	20-39	2	63	1 †		
	≥40	1	14	2.25	0.19 to 26.6	0.47
Breed	Small	2	26	0.86	0.18 to 4.11	1.00
	Medium	10	78	1.43	0.58 to 3.53	0.47
	Large	11	123	1 †		
Sex	Male	13	118	1.20	0.51 to 2.85	0.83
	Female	10	109	1 †		
Pregnancy status	Non-pregnant	10	100	1 †		
	Pregnant	0	9	0	0 to ∝	1.00
Habitus	Alert	1	79	1 †		
	Depressed	5	113	3.50	0.40 to 30.5	0.40
	Collapsed	17	35	38.4	4.91 to 300	<0.00001
Time since last meal	<1 day	10	125	1 †		
	1-3 days	9	78	1.44	0.56 to 3.71	0.47
	≥4 days	2	24	1.04	0.21 to 5.06	1.00
Vomiting	Absent	16	196	1 †		
	Present	7	28	3.06	1.16 to 8.10	0.03
Diarrhoea	Absent	19	198	1 †		
	Present	3	27	1.16	0.32 to 4.17	0.74
Neurological signs	Absent	21	221	1 †		
	Present	2	6	3.51	0.67 to 18.5	0.16
Icterus	Absent	15	203	1 †		
	Present	8	23	4.71	1.80 to 12.3	0.003
TOTAL		23	227			

* Odds ratio relative to reference category
† Reference category
§ *P*-value for Fisher's exact test

Table 4. Multiple logistic regression analysis of potential risk factors for hypoglycaemia in canine babesiosis

Factor	Category	β	OR	95% confidence interval	*P*
Age	<6 months	1.029	2.80	0.81 to 9.72	0.11
	6-11 months	-1.140	0.32	0.04 to 2.91	0.31
	≥12 months	0	1		
Haematocrit	<10	0.974	2.65	0.41 to 17.3	0.31
	10-19	-0.123	0.88	0.14 to 5.52	0.90
	20-39	0	1		
	≥40	0.491	1.63	0.11 to 24.3	0.72
Habitus	Alert	0	1		
	Depressed	0.828	2.29	0.24 to 21.5	0.47
	Collapsed	2.881	17.8	1.86 to 171	0.01
Vomiting	Present	0.422	1.53	0.46 to 5.07	0.50
Neurological signs	Present	-0.543	0.58	0.08 to 4.46	0.60
Icterus	Present	0.342	1.41	0.40 to 4.99	0.60

CHAPTER 5 DISCUSSION

5.1 PREVALENCE OF HYPOGLYCAEMIA

This study demonstrated that hypoglycaemia is an important and common complication of canine babesiosis caused by *Babesia canis rossi*. The prevalence of hypoglycaemia in falciparum malaria ranges from 5-32% in severely ill people.[40, 53] This finding is consistent with the prevalence of 19.8% found in severely ill dogs with babesiosis in this study (see Table 1).

An important factor to note is that a large percentage (69.9%) of the hypoglycaemic dogs had severe life-threatening hypoglycaemia (≤ 2.2 mmol/l). Five of these patients had a blood glucose concentration below 1.0 mmol/l. If severe hypoglycaemia is left untreated, the patient will go into a coma and ultimately die. For this reason results of the blood glucose concentrations of the patients were made known to the attending clinician. Patients with canine babesiosis are not routinely treated with dextrose and the findings in this study may challenge veterinarians to measure blood glucose concentrations routinely as is currently the practice with measuring the haematocrit in dogs with babesiosis.

5.2 PREVALENCE OF HYPERGLYCAEMIA

Hyperglycaemia was also common (15% of all cases and 19% of admitted cases), but was never severe. While more prevalent overall than hypoglycaemia, it was not a good indicator of severity of illness, since approximately half of the hyperglycaemic dogs did not require admission, while all but one of the hypoglycaemic cases did. The non-admitted hypoglycaemic case was only mildly hypoglycaemic (3.2 mmol/l).

Hyperglycaemia in critical illness is most often due to increased cortisol secretion.[69] In the context of a hypermetabolic illness such as babesiosis, hyperglycaemia was not a surprising finding. However, studies conducted in human medicine have shown that hyperglycaemia is considered an important prognostic indicator in the Intensive Care Unit (ICU) and insulin therapy is recommended even in patients with mild hyperglycaemia.[70] This may warrant further studies in the future in canine babesiosis.

5.3 SEVERITY OF DISEASE

Since hypoglycaemia is a sign of profound metabolic derangement,[15] we expected it to occur mainly in the severely ill dogs, which was indeed the case. Variables that were associated with a higher probability of hypoglycaemia ($P < 0.3$ in the univariable analysis) were clinical collapse, severe anaemia; age < 6 months, vomition and icterus (see Table 3).

Severe anaemia and icterus have been shown in previous studies to indicate severe disease and are some of the criteria used by a clinician to decide whether or not a patient should be admitted for further treatment.[9, 71]

5.4 HABITUS AND NEUROLOGICAL SIGNS

The variable showing the strongest association with hypoglycaemia in the multiple logistic regression model was habitus. A diagnosis of hypoglycaemia based on clinical signs poses obvious difficulties in babesiosis, since changes in level of consciousness, coma or seizures may be, and in the past have been, attributed to cerebral babesiosis.[7] Hypoglycaemia with associated neurological signs, especially collapse and seizures, is thus an important differential diagnosis for cerebral babesiosis.

Patients with severe anaemia and hypotension[72] may also present with altered levels of consciousness and these should also be evaluated in collapsed patients. Most hypoglycaemic dogs (91%) in this study did not show overt neurological signs (i.e. seizures) and only presented collapsed. Neurological signs reported in dogs with hypoglycaemia include[13, 33, 34]: amaurosis, hypothermia, localised reflex abnormalities, mental dullness, weakness, confusion, seizures and coma. The last two neurological signs are only seen in dogs with severe hypoglycaemia. Two dogs in this study presented with seizures. Both were hypoglycaemic and made a full recovery after intravenous dextrose administration.

Three collapsed (semi-comatose), hypoglycaemic dogs had severe miosis at presentation that corrected immediately after dextrose therapy. This finding has not been reported in the literature as a clinical sign of hypoglycaemia.

5.5 ANAEMIA

Although severe anaemia (Ht < 10) was strongly associated with hypoglycaemia in the univariate analysis ($P = 0.0002$), it was not significant in the logistic regression model ($P = 0.3$), probably because it was also strongly associated with age and habitus. Collapsed dogs were more likely to be severely anaemic than alert dogs (OR = 91, $P < 0.00001$), and dogs younger than 6 months were more likely to be severely anaemic than dogs older than one year (OR = 7, $P = 0.0009$).

The association between severe anaemia and hypoglycaemia can be explained in the first instance by the effects of hypoxia on glycolysis in that vastly more glucose is consumed during anaerobic glycolysis to produce the same ATP yield.

The severity of anaemia may also be related to the severity of the disease process and the inflammatory response, which can lead to hypermetabolism and excessive glucose consumption. Severe injury or infection is associated with enhanced cellular uptake of glucose.[18,19] During the inflammatory response, alterations in glucose and fat metabolism occur: the rate of gluconeogenesis increases, as do the rates of lactate and pyruvate formation. Glucose recycling from lactate and alanine accounts for much of

the increase in glucose production during stress. Although stress is typically associated with increased gluconeogenesis, there is evidence that septic stress is distinguished by a biphasic response. Lethal models of sepsis in animals demonstrate an initial phase of hyperglycaemia during which gluconeogenesis is increased, followed by a subsequent phase during which glucose production is suppressed and hypoglycaemia occurs.[15]

5.6 AGE

The finding that young age was a risk factor for hypoglycaemia was consistent with previous reports in humans and dogs. Hypoglycaemia is an important and common complication in children with malaria.[21, 40] Some studies in dogs have showed that puppies have lower blood glucose levels than adults.[56, 57] As mentioned earlier, hypoglycaemia in puppies is well documented, with an increased incidence seen in the toy breeds.[33, 58]

5.7 BREED

Although the predisposition of toy breeds to hypoglycaemia is well documented,[33, 59, 60] there was no association between breed and hypoglycaemia in this study. Twelve (42.9%) toy breed dogs were admitted due to severe/complicated babesiosis, but only two (7.1%) presented with hypoglycaemia.

5.8 ICTERUS

Hypoglycaemia was associated with icterus in this study although this was not significant in the logistic regression model. Both icterus and hypoglycaemia have been identified as indicators of life-threatening malaria.[52] Malherbe (1956) reported that haemolysis alone did not cause icterus in dogs with babesiosis.[73] Other studies supported this finding and suggested that icterus in canine babesiosis may not be just due to haemolysis, but also due to hepatic dysfunction.[8, 9]

Hepatic glycogenolysis is the primary source of glucose during short periods of fasting. After 24 hours of fasting, hepatic glycogen stores are depleted and gluconeogenesis then plays a greater role in the maintenance of euglycaemia.[13, 20] In patients that are icteric these pathways may not function adequately.

5.9 VOMITION

The presence of vomiting was significant in the univariate analysis, but not in the logistic regression model. This is a vague clinical sign with many potential causes and consequences. Patients that are vomiting lose nutrients, and may be less likely to eat and therefore have depleted glucose stores.

5.10 PREGNANCY

The absence of hypoglycaemia in the 9 pregnant bitches differs from human malaria, in which pregnancy is an important risk factor.[21, 40] This finding may be a function of the small number of pregnant bitches included in this study.

CHAPTER 6 CONCLUSIONS

Hypoglycaemia is a common and important complication of virulent canine babesiosis. Collapsed state and young age were the factors most strongly associated with hypoglycaemia, while severe anaemia, vomiting and icterus were also risk factors. Hypoglycaemia may previously have remained undiagnosed and untreated because coma, collapse and other neurological signs could be misinterpreted as shock and/or cerebral babesiosis.

Glucose should ideally be measured in all dogs with severe and complicated babesiosis, but is mandatory for dogs with the above risk factors. An instant method such as a dipstick or glucometer is recommended, to allow immediate diagnosis and correction of blood levels, if required.

The findings of the current study add to the numerous clinical similarities between canine babesiosis and human falciparum malaria.

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CONSENT FORM

Your dog has been diagnosed with tick fever/ biliary. At present we are conducting studies to evaluate the blood sugar (glucose) and blood lactate levels in dogs with babesiosis. This requires the collection of blood samples (±2ml of blood – half a teaspoon) taken at the time of diagnosis as well as on 3 occasions during the stay in hospital. At no time will the studies interfere with the treatment of your pet.

The costs of these tests will not be added to your account. We will be paying for the extra tests. However, you will still be responsible for other tests and the treatment of your dog.

This study has been passed by the Ethics Committee of the Faculty of Veterinary Science, University of Pretoria.

Thank you for your willingness to allow your animal to be entered into these studies. We hope that the information we gain will improve our understanding and treatment of babesiosis. Should you require more information please contact:

Dr N Keller or Dr M Nel
Companion Animal Medicine
Onderstepoort Veterinary Academic Hospital
Tel: 529-8000 or 529-8366 or 529-8094

I,……hereby give permission that my dog (name)……, a (colour)……, (sex)……, (breed)……, may participate in the clinical studies at the Onderstepoort Veterinary Academic Hospital. I understand that the studies will in no way harm my dog. Furthermore I understand that no additional costs will be incurred by me in respect of the trial for blood sampling and testing.

Signed at Onderstepoort on the …….. day of ……2001/2002.

Signature owner/authorised person ……..

Home tel: ……
Work tel: …….
Cell: ……

TOESTEMMINGSVORM

U hond is gediagnoseer met babesiose/ bosluiskoors/ galkoors. Op die oomblik is ons besig met studies wat die bloedsuiker (glukose) en bloedlaktaatvlakke ondersoek in honde met babesiose. Dit genoodsaak die neem van bloedmonsters (±2ml bloed – ‘n halwe teelepel) ten tye van diagnose asook gedurende hospitaalverblyf. Op geen stadium sal die studies inmeng met die behandeling van u hond nie.

Daar sal geen ekstra kostes by u rekening wees nie. Ons betaal vir die ekstra toetse. U sal wel verantwoordelik wees vir alle ander toetse en die behandeling van u hond.

Die studies is goedgekeur deur die Etiekkomitee van die Fakulteit Veeartsenykunde, Universiteit van Pretoria.

Dankie vir u bereidwilligheid om u hond in die studies toe te laat. Ons hoop dat die inligting wat ons gaan insamel, ons sal help om die siekte beter te verstaan en te behandel. As u meer wil weet kan u ons kontak by:

Dr N Keller of Dr M Nel
Geselskapsdiergeneeskunde
Onderstepoort Veterinêre Akademiese Hospitaal
Tel: 529-8000 of 529-8366 of 529-8094

Ek,…….gee hiermee toestemming dat my hond (naam)…….., ‘n (kleur)……., (geslag)…….., (ras)…… mag deelneem aan die kliniese studies by die Onderstepoort Veterinere Akademiese Hospitaal. Ek verstaan dat die studies geensins my hond sal benadeel nie. Verder verstaan ek dat daar geen ekstra kostes sal wees vir die neem en toets van die bloed vir die studies nie.

Geteken te Onderstepoort op die …… dag van ……..2001/2002.

Handtekening eienaar/gemagtigde persoon ……

Huis tel: ……
Werk tel: …….
Selfoon: ……

BREED CLASSIFICATION ACCORDING TO THE KENNEL UNION OF SOUTH AFRICA

The predominant breed was taken in crossbreeds. Breeds not seen during the study was not included in this list.

Toy Breeds:	Yorkshire Terrier
	Pomeranian
	Pekingese
	Chihuahua
	Maltese
	Miniature Doberman Pincher
Small and Medium:	Staffordshire Bullterrier
	Border Collie
	American Pit bullterrier
	Jack Russell Terrier
	Fox Terrier
	Daschund
	Bulldog
	Cocker Spaniel
	Cairn Terrier
Large and Giant:	German Shepherd Dog
	Boerboel
	Rhodesian Ridgeback
	Dalmatian
	Rottweiler
	Chow-chow
	Labrador Retriever
	Golden Retriever
	Boxer
	Husky
	Alaskan Malamute
	Great Dane
	St Bernard
	Belgium Shepherd
	Standard Poodle
	Doberman
	Bouvier de Flanders
	Rough Collie

*HYPOGLYCAEMIA and HYPERLACTATAEMIA IN CANINE BABESIOSIS HISTORY AND CLINICAL EXAMINATION FORM

Date:……

Owner:
Surname: ……Owner number:…….

Patient: Name:…… Number:……..

Age:…… Breed:…….

History Questionnaire

1.How long ago did you first notice that your dog was not well?

1day	2days	3days	>3 days

2.When was the last time your dog ate a full meal?

<1day	1-3days	4-6days	7+days

3. Did your dog vomit?

Yes	No

4. Does your dog have diarrhoea?(runny tummy)

Yes	No

5. Is your dog sterilised?

Yes	No

6. If your dog is a female, is she pregnant?

Yes	No

7. If yes – how far? _____

8. Was an ultrasound examination performed?:

Yes	No

9. If your dog is a female, does she have puppies at the moment?

Yes	No

10. How many puppies? _____

11. How old are the puppies?

< 2	2 – 4	4 – 6	> 6

* This questionare was used for another study as well and includes data that is not relevant to this study.

weeks	weeks	weeks	weeks

12.When last did you de-worm your dog?

Days ago	Weeks ago	Months ago	Years ago

13. Does your dog suffer from any medical condition:

Yes	No

14. If yes – specify: _____

15.Is your dog on any medication?

Yes	No

16. If yes – specify (drug, dose and route): _____

_____

Clinical findings

1.Habitus:

Alert	Depressed	Collapsed

2.Cerebral signs:

Yes	No

3. If yes – specify: _____

4.Visisble Icterus:

Yes	No

5.Respiratory rate:_____ Respiratory component:

Abdominal	Thoracic	Both

6.Micro-haematocrit:_____

7.In-saline-agglutination:

Pos.	Neg.

8.Blood lactate at presentation:_____mmol/L

9.Blood Glucose at presentation:_____mmol/L

HYPOGLYCAEMIA and HYPERLACTATAEMIA IN CANINE BABESIOSIS HISTORY AND CLINICAL EXAMINATION FORM

Date:……

Owner:

Surname: ……Owner number:…….

Patient: Name:……. Number:……..

Admitted: Time:……

Treatment: Diminazine, imidocarb, bloodtransfusion, ringers lactate, KCl, glucose, etc.

Date:	**Time:**	**Treatment:**	**Dose and route:**

Glucose level: **8hr:** **……** **mmol/l**

16hr: **……** **mmol/l**

24hr: **……** **mmol/l**

Lactate level: **8hr:** **……** **mmol/l**

16hr: **……** **mmol/l**

24hr: **……** **mmol/**l

Complications:

	YES	**NO**	**Not assessed**
Insaline agglutanation pos.:			
Respiratory distress:			
Cerebral:			
Icterus:			

Discharged: Date:…… Time:…….

Died: Date:…… Time:……

Euthanased: Date:…… Time:……..

Reason:

Cost	Poor prognosis	Other

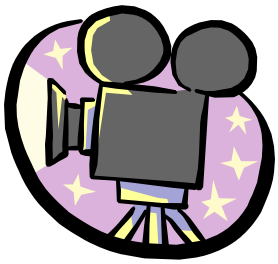
Specify:…….

Follow-up phone call: Date:……

Alive:

Yes	No

If no – specify:……



VIDEO CLIP

[See included CD on the back cover of this document (1:38 minutes long) - Microsoft Media Player needed to view clip.]

This is a short video clip of a 10kg, Corgi-cross called Charlie, who, on presentation, was collapsed with babesiosis. The only sign indicating that he was still alive was periodical blinking of his eyes.

He was also severely anaemic (PCV = 11%). A blood transfusion was started simultaneous to his blood glucose being measured. His blood glucose was 2.65 mmol/l. An iv bolus of 50% dextrose was administered at 0.5ml/kg (5ml in total).

Within 90 seconds after the administration of the dextrose bolus, Charlie responded favourably by wagging his tail and reacting to bystanders. The blood transfusion was only started a few minutes prior to the iv dextrose and could not have made such a tremendous difference within so short a period of time.

The video concludes by showing Charlie five hours later – after completion of the blood transfusion – in ICU and on the way to a full recovery.

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
1	56.0	1	3	<1 day	Yes	No	F	No	Collapsed	No	Yes	13	1.1	1_yes	yes
2	212.8	2	3	1-3 days	No	No	M	No	Collapsed	No	No	14	4.8	2_no	yes
3	1095.0	3	3	1-3 days		No	F	Yes	Collapsed	Yes	No	45	6.9	2_no	yes
4	1460.0	3	2	<1 day	No	No	F	No	Alert	No	No	20	5.9	2_no	no
5	1095.0	3	2	<1 day	No	No	F	No	Alert	No	No	40	4.3	2_no	no
6	70.0	1	2	<1 day	No	No	M	No	Collapsed	No	No	12	4.6	2_no	yes
7	365.0	3	3	<1 day	No	No	F	No	Alert	No	No	42	3.6	2_no	no
8	1095.0	3	1	1-3 days	No	No	F	Yes	Collapsed	No	No	13	5.4	2_no	no
9	1095.0	3	2	1-3 days	No	No	M	No	Alert	No	No	25	4.2	2_no	no
10	365.0	3	3	1-3 days	No	No	M	No	Alert	No	No	29	4.4	2_no	no
11	212.8	2	3	<1 day	No	No	F	No	Depressed	No	No	19	5.6	2_no	no
12	1460.0	3	3	4+ days	No	No	F	No	Depressed	No	No	21	4.9	2_no	no
13	121.6	1	3	4+ days	No	No	M	No	Depressed	No	Yes	15	4.4	2_no	no
14	273.6	2	3	1-3 days	No	No	M	No	Depressed	No	No	19	4.5	2_no	no
15	1095.0	3	3	1-3 days	No	No	M	No	Alert	No	No	12	5.7	2_no	no
16	121.6	1	3	<1 day	No	No	M	No	Depressed	No	No	16	5.4	2_no	no
17	304.0	2	3	<1 day	No	Yes	F	No	Depressed	No	No	27	5.0	2_no	no
18	730.0	3	3	1-3 days	No	No	M	No	Collapsed	No	No	9	5.6	2_no	yes
19	121.6	1	2	4+ days			M	No	Collapsed	No	No	6	3.7	2_no	yes
20	730.0	3	2	4+ days	No	No	F	No	Depressed	No	No	14	5.1	2_no	no
21	425.6	3	2	1-3 days	Yes	No	M	No	Depressed	No	No	42	4.5	2_no	no
22	273.6	2	3	1-3 days	No	No	M	No	Alert	No	No	19	5.6	2_no	no
23	2190.0	3	3	1-3 days	No	No	M	No	Alert	No	No	31	4.5	2_no	no
24	84.0	1	3	<1 day	No	No	M	No	Depressed	No	No	20	3.5	2_no	no
25	304.0	2	3	<1 day	No	No	M	No	Alert	No	No	20	4.5	2_no	no
26	730.0	3	3	1-3 days	No	No	F	No	Collapsed	No	Yes	9	1.2	1_yes	yes
27	2555.0	3	3	<1 day	No	No	M	No	Depressed	No	No	47	3.8	2_no	yes
28	547.5	3	3	4+ days	No	No	M	No	Collapsed	No	No	8	6.5	2_no	yes
29	212.8	2	3	1-3 days	No	Yes	M	No	Collapsed	No	No	11	6.2	2_no	yes
30	60.8	1	3	1-3 days	No	No	F	No	Depressed	No	No	10	2.1	1_yes	yes
31	212.8	2	3	<1 day	No	No	M	No	Depressed	No	No	14	5.6	2_no	no
32	243.2	2	2	1-3 days	No	No	F	No	Depressed	No	No	10	4.6	2_no	yes
33	136.8	1	2	<1 day	No	No	M	No	Depressed	No	No	29	6.0	2_no	no
34	2190.0	3	1	1-3 days	No	No	M	No	Depressed	No	No	55	2.5	1_yes	yes
35	243.2	2	3	1-3 days	No	No	F	No	Depressed	No	No	9	4.9	2_no	yes
36	547.5	3	3	4+ days	No	No	F	No	Depressed	No	No	18	5.4	2_no	no
37	182.4	2	2	1-3 days	No	No	F	No	Depressed	No	No	14	3.5	2_no	no
38	91.2	1	3	<1 day	No	Yes	M	No	Depressed	No	No	16	5.8	2_no	no
39	106.4	1	3	1-3 days	No	Yes	M	No	Collapsed	Yes	No	10	4.3	2_no	yes
40	912.5	3	3	1-3 days	No	No	F	No	Depressed	No	No	22	4.1	2_no	no
41	243.2	2	3	<1 day	No	No	M	No	Alert	No	No	22	5.2	2_no	no
42	1460.0	3	3	1-3 days	No	No	F	No	Depressed	No	No	18	5.0	2_no	no
43	730.0	3	2	4+ days	No	No	M	No	Depressed	No	No	10	4.2	2_no	no
44	5840.0	3	1	4+ days	Yes	No	M	No	Depressed	No	No	21	3.9	2_no	no
45	730.0	3	3	1-3 days	Yes	No	M	No	Depressed	No	No	21	4.5	2_no	no
46	730.0	3	3	4+ days	No	No	F	No	Depressed	No	No	10	3.8	2_no	no

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
47	91.2	1	3	1-3 days	Yes	No	M	No	Collapsed	Yes	No	10	0.5	1_yes	yes
48	547.5	3	3	<1 day	No	No	F	No	Depressed	No	No	14	3.1	1_yes	yes
49	2555.0	3	2	1-3 days	No	No	M	No	Depressed	No	No	18	5.4	2_no	no
50	304.0	2	2	4+ days	No	No	M	No	Depressed	No	Yes	12	3.7	2_no	yes
51	182.4	2	2	1-3 days	No	No	M	No	Depressed	No	No	10	5.2	2_no	yes
52	334.4	2	3	<1 day	No	No	F	No	Alert	No	No	38	6.0	2_no	no
53	912.5	3	3	<1 day	No	No	F	No	Depressed	No	No	9	4.0	2_no	no
54	182.4	2	2	<1 day	No	No	F	No	Collapsed	No	No	10	4.9	2_no	yes
55	1095.0	3	3	1-3 days	No	Yes	M	No	Collapsed	No	Yes	5	3.1	1_yes	yes
56	136.8	1	3	<1 day	No	No	F	No	Depressed	No	No	13	6.2	2_no	yes
57	273.6	2	2	1-3 days	No	No	F	No	Collapsed	No	No	9	4.5	2_no	yes
58	3285.0	3	3	<1 day	No	No	M	No	Depressed	No	No	38	3.9	2_no	no
59	730.0	3	3	<1 day	No	No	M	No	Depressed	No	No	9	5.9	2_no	no
60	182.4	2	3	<1 day	No	No	M	No	Alert	No	No	29	5.9	2_no	no
61	730.0	3	1	<1 day	No	Yes	F	No	Alert	No	No	26	4.5	2_no	no
62	5475.0	3	3	1-3 days	No	No	F	No	Depressed	No	No	28	4.6	2_no	no
63	243.2	2	2	4+ days	Yes	Yes	F	Yes	Depressed	No	No	23	5.3	2_no	yes
64	547.5	3	3	<1 day	No	No	F	No	Depressed	No	No	17	4.8	2_no	no
65	121.6	1	3	<1 day	No	No	M	No	Depressed	No	No	7	7.0	2_no	yes
66	121.6	1	3	<1 day	No	No	F	No	Depressed	No	No	11	5.4	2_no	yes
67	60.8	1	1	<1 day	No	No	F	No	Depressed	No	No	8	6.0	2_no	yes
68	182.4	2	3	<1 day	Yes	Yes	F	No	Depressed	No	No	16	5.1	2_no	no
69	365.0	3	2	<1 day	No	No	M	No	Depressed	No	No	33	4.6	2_no	no
70	730.0	3	2	<1 day	No	No	M	No	Depressed	No	No	15	4.5	2_no	no
71	91.2	1	3	<1 day	Yes	No	M	No	Depressed	No	No	8	1.7	1_yes	yes
72	547.5	3	3	1-3 days	No	No	M	No	Depressed	No	No	17	4.6	2_no	no
73	1460.0	3	3	1-3 days	No	No	F	No	Depressed	No	No	22	4.6	2_no	no
74	2555.0	3	3	<1 day	No	No	M	No	Depressed	No	No	20	5.4	2_no	no
75	1460.0	3	3	<1 day	No	No	F	No	Collapsed	No	No	25	3.5	2_no	yes
76	365.0	3	3	<1 day	No	No	F	No	Depressed	No	No	25	3.6	2_no	no
77	730.0	3	3	<1 day	No	No	F	No	Depressed	No	No	19	4.4	2_no	no
78	212.8	2	2	1-3 days	No		F	No	Collapsed	No	Yes	5	2.2	1_yes	yes
79	1460.0	3	3	<1 day	No	No	M	No	Depressed	No	No	19	5.3	2_no	no
80	304.0	2	3	1-3 days	No	No	F	No	Depressed	No	No	18	5.1	2_no	no
81	1095.0	3	2	1-3 days	No	No	F	No	Depressed	No	No	17	5.5	2_no	no
82	273.6	2	1	<1 day	Yes	Yes	F	No	Depressed	No	Yes	13	3.8	2_no	yes
83	365.0	3	2	<1 day	No	No	F	No	Depressed	No	No	22	4.7	2_no	no
84	182.4	2	2	1-3 days	No	No	F	No	Depressed	No	No	9	5.7	2_no	no
85	2190.0	3	3	<1 day	No	No	F	No	Alert	No	No	27	3.4	2_no	no
86	365.0	3	1	1-3 days	No	No	M	No	Collapsed	No	Yes	8	5.7	2_no	no
87	365.0	3	3	1-3 days	No	No	M	No	Collapsed	No	Yes	7	5.6	2_no	yes
88	182.4	2	3	<1 day	No	No	F	No	Depressed	No	No	15	5.3	2_no	no
89	121.6	1	3	<1 day	No	No	M	No	Depressed	No	No	11	4.2	2_no	yes
90	182.4	2	3	<1 day	No	No	F	No	Depressed	No	No	13	5.3	2_no	no
91	1460.0	3	2	<1 day	Yes	No	F	No	Collapsed	No	No	11	2.3	1_yes	yes
92	91.2	1	3	<1 day	No	No	M	No	Depressed	No	No	10	3.4	2_no	no

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
93	152.0	1	1	1-3 days	No	No	M	No	Depressed	No	No	14	4.4	2_no	no
94	2372.5	3	2	<1 day	No	No	F	No	Alert	No	No	31	4.7	2_no	no
95	60.8	1	1	<1 day	No	No	M	No	Alert	No	No	11	7.3	2_no	no
96	1095.0	3	2	1-3 days	No	Yes	M	No	Depressed	No	No	15	6.7	2_no	yes
97	1095.0	3	2	1-3 days	No	No	F	Yes	Depressed	No	No	12	4.2	2_no	yes
98	182.4	2	2	1-3 days	No	No	F	No	Alert	No	No	18	5.6	2_no	no
99	365.0	3	3	<1 day	No	No	M	No	Alert	No	No	23	4.9	2_no	no
100	730.0	3	2	4+ days	No	No	M	No	Collapsed	No	No	9	2.5	1_yes	yes
101	2555.0	3	2	<1 day	No	No	F	No	Alert	No	No	29	3.9	2_no	no
102	212.8	2	3	<1 day	No	No	M	No	Collapsed	No	No	9	6.0	2_no	yes
103	365.0	3	2	<1 day	No	No	M	No	Depressed	No	No	19	5.4	2_no	no
104	365.0	3	3	<1 day	No	No	F	No	Collapsed	No	No	10	0.7	1_yes	yes
105	730.0	3	1	<1 day	Yes	No	F	No	Depressed	No	No	26	3.8	2_no	no
106	365.0	3	2	<1 day	No	No	F	No	Depressed	No	No	9	4.2	2_no	yes
107	365.0	3	2	<1 day	No	No	F	No	Depressed	No	No	12	4.4	2_no	no
108	912.5	3	2	<1 day	No	No	M	No	Alert	No	No	16	4.5	2_no	no
109	182.4	2	2	1-3 days	No	No	M	No	Alert	No	No	18	5.3	2_no	no
110	152.0	1	2	<1 day	No	No	F	No	Alert	No	No	13	4.5	2_no	yes
111	3285.0	3	1	<1 day	No	No	F	No	Alert	No	No	53	3.9	2_no	yes
112	365.0	3	2	<1 day	No	No	F	No	Alert	No	No	27	4.5	2_no	no
113	1095.0	3	3	1-3 days	No	No	F	No	Alert	No	No	11	4.8	2_no	yes
114	584.0	3	3	1-3 days	No	No	F	Yes	Depressed	No	No	15	4.8	2_no	yes
115	28.0	1	3	<1 day	No	No	F	No	Depressed	No	No	11	7.0	2_no	yes
116	1825.0	3	2		Yes	Yes	F	No	Collapsed	No	No	24	2.0	1_yes	yes
117	3650.0	3	3	1-3 days	No	No	F	No	Depressed	No	No	25	5.2	2_no	no
118	2555.0	3	3	1-3 days	No	No	M	No	Alert	No	No	20	5.2	2_no	no
119	730.0	3	1	<1 day	No	No	M	No	Alert	No	No	20	4.6	2_no	no
120	2190.0	3	3	<1 day	No	No	M	No	Depressed	No	No	21	4.6	2_no	no
121	1825.0	3	2	<1 day	No	No	M	No	Depressed	No	Yes	13	9.5	2_no	yes
122	70.0	1	3	4+ days	Yes	Yes	F	No	Depressed	No	No	10	4.8	2_no	yes
123	121.6	1	3	1-3 days	No	Yes	M	No	Depressed	No	No	14	4.6	2_no	no
124	182.4	2	2	1-3 days	No	Yes	M	No	Depressed	No	No	11	5.3	2_no	no
125	730.0	3	3	1-3 days	No	No	M	No	Depressed	No	No	20	4.8	2_no	no
126	365.0	3	3	1-3 days	No	No	M	No	Depressed	No	No	12	4.3	2_no	yes
127	1825.0	3	3	<1 day	No	No	M	No	Depressed	No	No	11	5.0	2_no	no
128	334.4	2	3	1-3 days	No	No	M	No	Depressed	No	No	16	5.4	2_no	no
129	456.0	3	3	1-3 days	No	No	M	No	Depressed	No	No	17	3.5	2_no	no
130	365.0	3	1	<1 day	No	No	F	No	Depressed	No	No	9	3.4	2_no	yes
131	243.2	2	3	<1 day	No	No	F	No	Depressed	No	No	11	4.2	2_no	yes
132	4015.0	3	2	<1 day	No	No	F	Yes	Collapsed	Yes	No	41	3.4	2_no	no
133	152.0	1	3	<1 day	No	No	F	No	Alert	No	No	10	5.9	2_no	no
134	365.0	3	2	4+ days	No	No	F	No	Alert	No	No	13	4.4	2_no	yes
135	1095.0	3	3	1-3 days	No	No	M	No	Alert	No	No	58	3.9	2_no	yes
136	730.0	3	3	<1 day	No	Yes	F	No	Alert	No	No	6	6.8	2_no	yes
137	3650.0	3	1	<1 day	No		F	No	Depressed	No	No	30	4.3	2_no	no
138	949.0	3	2	1-3 days	No	No	M	No	Depressed	No	No	10	5.0	2_no	no

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
139	365.0	3	2	1-3 days	No	No	M	No	Collapsed	No	Yes	14	4.2	2_no	yes
140	91.2	1	3	<1 day	Yes	No	F	No	Depressed	No	No	9	4.9	2_no	no
141	304.0	2	2	<1 day	No	Yes	M	No	Alert	No	No	34	4.5	2_no	no
142	365.0	3	3	<1 day	No	No	M	No	Alert	No	No	26	4.9	2_no	no
143	1679.0	3	3	<1 day	No	No	M	No	Alert	No	No	10	4.2	2_no	yes
144	304.0	2	3	4+ days	Yes	Yes	F	No	Alert	No	No	13	3.9	2_no	no
145	730.0	3	2	1-3 days	Yes	No	F	No	Alert	No	No	23	5.0	2_no	no
146	182.4	2	1	1-3 days	Yes	Yes	M	No	Depressed	No	No	13	4.4	2_no	yes
147	3285.0	3	1	1-3 days	Yes	No	M	No	Depressed	No	No	12	5.3	2_no	yes
148	152.0	1	2	1-3 days	No	No	M	No	Alert	No	No	13	5.3	2_no	no
149	1095.0	3	3	<1 day	No	No	F	No	Alert	No	No	22	5.0	2_no	no
150	730.0	3	2	<1 day	No	No	M	No	Depressed	No	No	9	5.1	2_no	yes
151	1460.0	3	2	1-3 days		No	F	No	Depressed	No	No	19	4.1	2_no	no
152	365.0	3	3	4+ days	No	No	M	No	Collapsed	No	No	9	5.8	2_no	yes
153	365.0	3	3	1-3 days	Yes	Yes	M	No	Collapsed	No	Yes	12	10.3	2_no	yes
154	3650.0	3	2	<1 day	No	No	M	No	Depressed	No	No	22	4.1	2_no	no
155	91.2	1	3	<1 day	Yes	No	F	No	Collapsed	No	No	9	5.6	2_no	yes
156	2190.0	3	3	1-3 days	Yes	Yes	F	No	Collapsed	No	No	41	3.6	2_no	yes
157	365.0	3	2	1-3 days	No	No	F	No	Depressed	No	No	13	4.5	2_no	yes
158	121.6	1	3	1-3 days	No	No	M	No	Collapsed	No	No	10	4.5	2_no	yes
159	1460.0	3	3	<1 day	No	No	F	No	Alert	No	No	55	3.3	2_no	yes
160	730.0	3	3	4+ days	No	No	M	No	Collapsed	No	Yes	8	1.9	1_yes	yes
161	56.0	1	3	<1 day	No	No	M	No	Alert	No	No	16	5.5	2_no	yes
162	121.6	1	3	<1 day	No	No	M	No	Depressed	No	No	12	5.2	2_no	yes
163	730.0	3	2	<1 day	No	No	M	No	Depressed	No	No	17	4.7	2_no	yes
164	121.6	1	3	<1 day	No	Yes	M	No	Depressed	No	Yes	13	3.5	2_no	yes
165	1460.0	3	2		Yes	Yes	M	No	Collapsed	No	Yes	9	2.8	1_yes	yes
166	91.2	1	1	4+ days	No	Yes	F	No	Collapsed	Yes	Yes	10	4.2	2_no	yes
167	304.0	2	3	<1 day	No	No	M	No	Alert	No	No	15	4.8	2_no	no
168	273.6	2	3	<1 day	No	No	F	No	Alert	No	No	16	4.7	2_no	no
169	511.0	3	2	<1 day	No	No	F	No	Alert	No	No	19	4.6	2_no	no
170	912.5	3	2	<1 day	No	No	M	No	Alert	No	No	26	4.9	2_no	no
171	1314.0	3	2	<1 day	No	No	M	No	Alert	No	No	10	3.6	2_no	no
172	91.2	1	2	<1 day	No	No	M	No	Depressed	No	No	13	4.0	2_no	no
173	2920.0	3	2	1-3 days	No	No	M	No	Depressed	No	No	13	6.0	2_no	yes
174	91.2	1	3	<1 day	No	No	M	No	Depressed	No	No	13	5.3	2_no	yes
175	334.4	2	3	4+ days	Yes	No	F	No	Depressed	No	No	9	4.8	2_no	yes
176	1825.0	3	3	4+ days	No	Yes	M	No	Alert	No	No	20	4.1	2_no	no
177	365.0	3	3	<1 day	No	No	F	No	Alert	No	No	18	4.0	2_no	no
178	1095.0	3	3	1-3 days	No	No	M	No	Depressed	No	No	16	4.3	2_no	yes
179	3650.0	3	3	4+ days	No	No	M	No	Collapsed	No	Yes	11	9.8	2_no	yes
180	152.0	1	3	<1 day	Yes	Yes	M	No	Collapsed	Yes	No	32	5.7	2_no	yes
181	49.0	1	3	1-3 days	Yes	Yes	M	No	Collapsed	No	No	11	5.4	2_no	yes
182	730.0	3	2	<1 day	No	No	M	No	Collapsed	No	Yes	7	3.4	2_no	yes
183	365.0	3	2	<1 day	No	Yes	F	No	Alert	No	Yes	6	4.5	2_no	yes
184	365.0	3	3	<1 day	Yes	No	F	No	Collapsed	No	Yes	10	5.0	2_no	yes

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
185	212.8	2	2	<1 day	No	No	F	Yes	Alert	No	No	26	4.6	2_no	no
186	2920.0	3	3	<1 day	Yes	No	M	No	Alert	No	No	21	4.0	2_no	no
187	730.0	3	1	<1 day	Yes	No	F	No	Depressed	No	No	8	4.8	2_no	no
188	365.0	3	1	<1 day	No	No	M	No	Alert	No	No	20	3.7	2_no	no
189	3285.0	3	2	1-3 days	No	No	F	No	Collapsed	No	No	8	4.4	2_no	yes
190	3285.0	3	3	1-3 days	No	No	F	No	Depressed	No	No	32	4.4	2_no	no
191	91.2	1	3	1-3 days	No	No	F	No	Alert	No	No	12	4.4	2_no	no
192	121.6	1	3	<1 day	No	No	M	No	Collapsed	Yes	No	9	0.3	1_yes	yes
193	2555.0	3	1	1-3 days	No	No	F	No	Depressed	No	Yes	13	6.2	2_no	yes
194	121.6	1	3	<1 day	No	Yes	M	No	Depressed	No	No	8	4.1	2_no	yes
195	730.0	3	2	<1 day	No	No	F	No	Alert	No	No	15	4.5	2_no	no
196	365.0	3	3	<1 day	No	No	F	Yes	Depressed	No	No	32	5.5	2_no	no
197	182.4	2	1	<1 day	No	No	M	No	Alert	No	No	10	4.8	2_no	no
198	1825.0	3	1	1-3 days	No	No	M	No	Alert	No	No	27	5.5	2_no	yes
199	365.0	3	2	<1 day	No	No	F	No	Alert	No	No	11	5.0	2_no	yes
200	1095.0	3	2	<1 day	No	No	F	No	Alert	No	No	32	4.8	2_no	no
201	1095.0	3	2	<1 day	No	No	M	No	Alert	No	No	10	4.7	2_no	no
202	365.0	3	3	<1 day	No	No	M	No	Depressed	No	No	33	4.5	2_no	no
203	1095.0	3	2	1-3 days	Yes	No	M	No	Collapsed	No	Yes	7	3.8	2_no	yes
204	273.6	2	2	<1 day	No	No	F	No	Alert	No	No	26	3.7	2_no	no
205	730.0	3	3	<1 day	No	No	F	No	Alert	No	No	12	5.0	2_no	yes
206	3650.0	3	1	<1 day	No	No	F	No	Depressed	No	No	13	4.5	2_no	no
207	1825.0	3	2	<1 day	No	No	M	No	Alert	No	No	23	5.0	2_no	no
208	365.0	3	2	4+ days	No	No	M	No	Depressed	No	No	10	4.8	2_no	no
209	91.2	1	1	1-3 days	No	No	M	No	Depressed	No	No	7	1.8	1_yes	yes
210	365.0	3	1	<1 day	No	No	F	No	Alert	No	No	20	3.7	2_no	no
211	1460.0	3	1	1-3 days	No	No	M	No	Depressed	No	No	22	4.5	2_no	no
212	273.6	2	2	1-3 days	Yes	No	M	No	Alert	No	No	10	4.1	2_no	yes
213	730.0	3	3	1-3 days	No	No	M	No	Collapsed	No	Yes	8	2.1	1_yes	yes
214	121.6	1	3	<1 day	No	Yes	M	No	Depressed	No	No	20	4.7	2_no	no
215	365.0	3	3	1-3 days	No	No	F	No	Alert	No	No	12	3.8	2_no	no
216	365.0	3	3	<1 day	No	No	M	No	Depressed	No	No	24	4.1	2_no	no
217	1095.0	3	2	1-3 days	No	No	F	No	Depressed	No	No	40	3.4	2_no	no
218	1095.0	3	2	<1 day	No	No	F	No	Alert	No	No	20	3.8	2_no	no
219	365.0	3	2	1-3 days	No	No	F	No	Alert	No	No	45	3.3	2_no	no
220	243.2	2	3	<1 day	No	No	M	No	Alert	No	No	11	5.4	2_no	yes
221	4745.0	3	2	1-3 days	No	No	M	No	Depressed	No	Yes	10	6.4	2_no	yes
222	121.6	1	2	<1 day	No	No	M	No	Collapsed	No	No	11	1.6	1_yes	yes
223	2555.0	3	3	<1 day	No	No	F	No	Depressed	No	No	20	4.4	2_no	no
224	182.4	2	2	1-3 days	No	No	F	No	Depressed	No	Yes	10	5.7	2_no	no
225	121.6	1	3	<1 day	Yes	No	M	No	Collapsed	No	No	19	3.4	2_no	yes
226	2920.0	3	3	1-3 days	No	No	F	No	Alert	No	No	13	5.0	2_no	yes
227	730.0	3	3	<1 day	Yes	No	M	No	Alert	No	No	12	4.2	2_no	no
228	212.8	2	2	<1 day	No	No	F	No	Depressed	No	Yes	10	4.7	2_no	yes
229	1825.0	3	1	1-3 days	No	No	F	No	Collapsed	No	No	10	5.3	2_no	yes
230	1095.0	3	2	<1 day	No	No	M	No	Depressed	No	Yes	10	4.6	2_no	yes

Order	AgeDays	AgeGroup	Breed	NotEat2	Vomit	Diarr	Sex	Pregnant	Habitus	Cerebral	Icterus	Ht	Glucose	Hypoglyc	Admitted
231	365.0	3	2	<1 day	No	No	F	No	Alert	No	No	35	3.6	2_no	no
232	121.6	1	2	1-3 days	No	No	M	No	Collapsed	No	Yes	6	2.2	1_yes	yes
233	365.0	3	2	1-3 days	No	No	F	No	Alert	No	No	11	4.8	2_no	yes
234	35.0	1	2	<1 day	No	No	F	No	Collapsed	No	No	10	0.1	1_yes	yes
235	2190.0	3	3	4+ days	No	No	M	No	Alert	No	Yes	15	4.6	2_no	yes
236	1460.0	3	3	1-3 days	No	No	M	No	Alert	No	No	42	3.9	2_no	no
237	1460.0	3	3	1-3 days	No	Yes	F	No	Alert	No	No	9	4.7	2_no	yes
238	121.6	1	2	<1 day	Yes	No	M	No	Collapsed	No	No	7	0.5	1_yes	yes
239	1825.0	3	2	<1 day	No	No	F	No	Alert	No	No	32	3.2	1_yes	no
240	730.0	3	3	4+ days	No	No	M	No	Alert	No	No	15	5.3	2_no	no
241	1460.0	3	3	<1 day	No	No	M	No	Collapsed	No	No	8	4.0	2_no	yes
242	1825.0	3	2	<1 day	No	No	M	No	Alert	No	No	22	4.4	2_no	no
243	28.0	1	2	<1 day	No	No	M	No	Depressed	No	No	5	5.2	2_no	yes
244	1460.0	3	3	<1 day	Yes	No	M	No	Alert	No	No	21	5.3	2_no	no
245	63.0	1	3	4+ days	No	No	M	No	Collapsed	No	Yes	5	5.6	2_no	yes
246	730.0	3	3	4+ days	No	No	F	No	Depressed	No	No	15	5.3	2_no	no
247	182.4	2	2	<1 day	No	No	F	No	Alert	No	No	13	4.1	2_no	no
248	365.0	3	3	<1 day	No	No	F	Yes	Collapsed	Yes	No	52	3.9	2_no	no
249	365.0	3	3	<1 day	No	No	F	No	Depressed	No	Yes	10	4.8	2_no	no
250	212.8	2	1	<1 day	Yes	No	F	No	Alert	No	No	20	4.3	2_no	no

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Prevalence and Risk Factors of Hypoglycemia in Virulent Canine Babesiosis

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Hypoglycemia is a common complication of virulent canine babesiosis. A study was conducted to determine the prevalence of and potential risk factors for hypoglycemia in canine babesiosis from *Babesia canis rossi*. Plasma glucose concentration was measured at presentation in 250 dogs with babesiosis, of which 111 were admitted to hospital. The prevalence of hypoglycemia (<60 mg/dL) was 9% (23/250). Twenty-two hypoglycemic dogs required admission, making the prevalence of hypoglycemia in admitted dogs 19.8%. Sixteen dogs had severe hypoglycemia (<40 mg/dL), of which 5 had glucose < 18 mg/dL. Hyperglycemia (>100 mg/dL) was present in 38 dogs, of which 21 were admitted. Risk factors for hypoglycemia identified by univariate analysis were collapsed state ($P < .00001$), severe anemia ($P = .0002$), icterus ($P = .003$), age <6 months ($P = .02$), and vomiting ($P = .03$). After logistic regression analysis, collapsed state (odds ratio [OR] = 18; 95% CI, 1.9–171; $P = .01$) and young age (OR = 2.8; 95% CI, 0.8–9.7; $P = .1$) remained significantly associated with hypoglycemia. Toy breeds and pregnant bitches were not at higher risk for hypoglycemia than other dogs. Blood glucose concentration should ideally be measured in all dogs requiring inpatient treatment for babesiosis but is mandatory in collapsed dogs; puppies; and dogs with severe anemia, vomiting, or icterus. Many dogs have probably been misdiagnosed with cerebral babesiosis in the past, and hypoglycemia should be suspected in any dog with coma or other neurological signs.

Key words: Anemia; *Babesia*; icterus; neurology; vomiting.

Canine babesiosis is a tick-borne disease caused by the hemoprotozoan parasite *Babesia canis*.[1] Babesiosis is a common cause of morbidity and mortality of dogs in South Africa, accounting for 12% of dogs presenting at the Onderstepoort Veterinary Academic Hospital and for approximately 12% of canine mortalities seen by private veterinarians in South Africa.[2,3] Babesiosis can range from a very mild to a peracutely fatal disease.[4] The parasite primarily affects the erythrocytes, with hemolytic anemia being a hallmark of the disease,[5] but multiple organ involvement also occurs.[6]

The similarities between virulent canine babesiosis and falciparum malaria in humans have long been noted. Both diseases are characterized by anemia and share very similar complications.[7] Malaria research can therefore provide a basis for research in canine babesiosis.[8] Hypoglycemia in malaria is a well-described finding and was documented as early as 1944.[9–13] Several contributing factors have been implicated and include increased peripheral requirement for glucose during febrile and critical illness,[7,14,15] obligatory demands of the parasites that use glucose as their major fuel,[16] hyperinsulinemia (often attributed to quinine administration),[17,18] failure of hepatic gluconeogenesis and glycogenolysis,[19,20] and increased glucose consumption by anaerobic glycolysis because of tissue hypoxia. Hypoglycemia is a serious and common complication of *Plasmodium falciparum* malaria, particularly in children[9] and pregnant women,[21] and is associated with a poor prognosis.[11,22–24] Response to treatment is variable, and intravenous dextrose does not reliably improve glycemic status or survival.[9,10,24,25]

Several reports of mild to severe hypoglycemia have been published in dogs with critical illness,[26,27] endotoxic shock,[28] sepsis,[29,30] parvoviral enteritis,[31–33] and nonspecific severe diarrhea,[32] as well as in endocrinopathies, particularly insulinoma.[26] Alterations in blood glucose represent one of the most consistent findings in canine sepsis.[26,27,34] Failure of energy production in sepsis is associated with impaired gluconeogenesis and decreased glycogenolysis secondary to depletion of hepatic and muscle glycogen stores.[15,35] A direct relationship between blood glucose concentrations and survival in critically ill dogs has been reported.[29,36,37]

Certain animals might be at higher risk for hypoglycemia. Symptomatic and even fatal hypoglycemia is well recognized in severely malnourished or fasted children[38] and has also been reported in dogs.[39] Hypoglycemia can also occur in pregnant and lactating bitches, usually during late pregnancy and early postpartum.[39,40] Toy breeds (Poodles, Yorkshire Terriers, Chihuahuas) are more prone to hypoglycemia, especially during periods of stress or fasting.[39,41,42]

Hypoglycemia has recently been identified as a potentially important complication of canine babesiosis in South Africa[a]. Five of 20 dogs with severe or complicated babesiosis had plasma glucose <60 mg/dL. There were striking clinical and biochemical differences between the hypoglycemic and normoglycemic dogs. The hypoglycemic dogs had a lower hematocrit, higher blood lactate concentration, and high fatality rate.

No studies have previously been conducted to determine the prevalence of hypoglycemia in canine babesiosis, despite the possibility that it can be a life-threatening complication. The main aims of this study were to determine the prevalence of hypoglycemia in canine babesiosis and to determine potential risk factors.

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Materials and Methods

Two hundred fifty dogs with clinical babesiosis that presented sequentially at the Onderstepoort Veterinary Academic Hospital over a 3-month period were prospectively included in the study. Babesiosis was diagnosed by the presence of parasites on a thin stained[b] capillary blood smear in association with typical clinical signs.

Age, sex, and breed (classified into toy, small and medium, large and giant according to the Kennel Union of South African guidelines) were recorded. Owners completed a questionnaire about the time since last full meal, vomiting, diarrhea, and pregnancy status. The admission microhematocrit was recorded. The data collector (NK, MN, or MdeC) performed a full clinical examination and noted the presence or absence of clinical icterus (yellow mucus membranes) and neurological signs (eg, coma, ataxia, seizures) and also documented the mental status (collapsed, depressed, or alert).

Blood was collected before treatment from all dogs by the cephalic or jugular vein into an evacuated glass tube containing sodium fluoride potassium oxalate.[c] Samples were centrifuged (1,730 × *g*) for 10 minutes, and the serum was separated. Where possible, plasma glucose was measured within 15 minutes. These results were only made available after the attending clinician had decided whether or not the dog should be admitted, thereby avoiding bias. Where necessary, samples were stored at 4°C for up to 3 days. Glucose is stable under these conditions.[43] Glucose was measured by the hexokinase method.[d,43,44]

The sample size of 250 was determined by PASS[45] software on a personal computer. Calculations were based on an expected prevalence of hypoglycemia of 6% in dogs with babesiosis (Jacobson, personal communication), with a confidence level of 95% and an absolute error of 3%.

Hypoglycemia in this study was defined as a blood glucose concentration <60 mg/dL[46–48] and hyperglycemia as >100 mg/dL. Glucose concentrations <40 mg/dL were classified as severe hypoglycemia.[39,49]

Age, hematocrit, breed, sex, pregnancy status, mental status, time since last meal, history of vomiting or diarrhea, neurological signs, and icterus were assessed for their usefulness as predictors of hypoglycemia. Patients were classified into discrete, clinically meaningful categories of each predictor variable. Descriptive statistics included the mean and median blood glucose concentrations for each category of each predictor variable. The medians for each category of a variable were compared by Kruskal-Wallis 1-way analysis of variance on ranks. The prevalence of hypoglycemia, with 95% confidence intervals, was calculated for admitted and nonadmitted dogs.

Univariate analysis of each predictor variable was performed for the binary outcome (hypoglycemia) with contingency tables and the Fisher exact test. Variables with $P < .3$ on univariate analysis were selected for testing in a multivariate logistic regression model, which was then developed by backward elimination. Variables remained in the model if they (or, in the case of polytomous predictor variables, at least 1 of their design variables) were significant in the model (Wald $P < .1$) or if their removal resulted in a >10% change in the effect of other variables. Statistical analysis was done on a personal computer by NCSS software.[45]

Results

Nine percent (23/250) of the dogs presenting with babesiosis were hypoglycemic at presentation (Table 1). Almost half (111/250; 44.4%) of the dogs were considered to be severely ill by the attending clinician and were admitted to the Intensive Care Unit. Twenty-two (95.7%) of the hypoglycemic dogs fell into this category.

There were significant differences in plasma glucose concentration between predictor levels (Table 2). Data are incomplete where owners did not know all the answers to the questionnaire. Sixteen dog (69.6% of hypoglycemic dogs; 14.4% of all admitted dogs) had severe hypoglycemia (<40 mg/dL). Five of these (21.7% of hypoglycemic dogs; 4.5% of admitted dogs) had blood glucose concentrations <18 mg/dL.

Table 1. Prevalence of hypoglycemia (plasma glucose <60 mg/dl) in dogs presented with canine babesiosis.

	n	Prevalence[a] (%)	95% CI
Admitted cases	22/111	19.8 A	13.1–28.7
Nonadmitted cases	1/139	0.72 B	0.04–4.54
Total	23/250	9.20	6.1–13.7

[a] Prevalence with different letters differs significantly between groups (Fisher exact test, $P < .00001$).

Fifteen percent (38/250) of dogs had hyperglycemia at the time of presentation. Only 55% (21/38) of hyperglycemic dogs were ill enough to warrant admission, thus making up roughly the same proportion as hypoglycemic dogs in the admitted group. The highest blood glucose concentration was 186 mg/dL.

The variables selected ($P < .3$) for inclusion in the multiple logistic regression model were age, hematocrit, mental status, vomiting, neurological signs, and icterus (Tables 3, 4). Predictor variables significant in the model were mental status ($P = .01$) and age ($P = .1$). Collapsed dogs were 17.8 times more likely to be hypoglycemic than alert dogs, and dogs <6 months old were 2.8 times more likely to be hypoglycemic than dogs >1 year old. The other variables remained in the model as confounders.

Discussion

This study demonstrated that hypoglycemia is an important and common complication of canine babesiosis caused by *B. canis rossi*. The prevalence of hypoglycemia in falciparum malaria ranges from 5 to 32% in severely ill people.[9,24] This is consistent with the prevalence of 19.8% found in severely ill dogs with babesiosis in this study.

Hyperglycemia was also common (15% of all dogs; 19% of admitted dogs) but was never severe. Although more prevalent overall than hypoglycemia, it was not a good indicator of severity of illness because approximately half of the hyperglycemic dogs did not require admission, whereas all but 1 of the hypoglycemic dogs did. Hyperglycemia in critical illness most often is caused by increased glucose mobilization,[15] and stress and can be markedly increased by increased cortisol secretion.[50] In the context of a hypermetabolic illness such as babesiosis, hyperglycemia was not a surprising finding.

Because hypoglycemia is a sign of profound metabolic derangement,[15] we expected it to occur mainly in the severely ill dogs, which was indeed the case. Variables that were associated with a higher probability of hypoglycemia ($P < .05$ in the univariate analysis) were clinical collapse, severe anemia, age < 6 months, vomiting, and icterus (see Table 3). The variable showing the strongest association with hypoglycemia in the multiple logistic regression model was mental status. Although a detailed description of the

Table 2. Plasma glucose concentration and putative risk factors in canine babesiosis.[a]

Variable	Category	n	Blood Glucose Concentration (mg/dl)	
			Median	Range
Age	<6 months	49	81.0 ab	2.0–131
	6–11 months	47	88.2 a	39.6–111
	≥12 months	154	81.0 b	12.6–185
Hematocrit	<10	43	81.0 ab	5.4–126
	10–19	125	86.4 a	2.0–185
	20–39	65	81.0 a	36.0–108
	≥40	15	68.4 b	45.0–124
Breed	Small	28	80.1 a	32.4–131
	Medium	88	81.0 a	2.0–171
	Large	134	86.4 a	5.4–185
Sex	Male	131	82.8 a	5.4–185
	Female	119	81.0 a	2.0–126
Pregnancy status	Nonpregnant	110	81.0 a	2.0–126
	Pregnant	9	86.4 a	61.2–124
Mental status	Alert	80	81.9 ab	57.6–131
	Depressed	118	84.6 a	30.6–171
	Collapsed	52	73.8 b	2.0–185
Time since last meal	<1 day	135	82.8 a	2.0–171
	1–3 days	87	82.8 a	9.0–185
	≥4 days	26	84.6 a	34.2–176
Vomiting	Absent	212	82.8 a	2.0–176
	Present	35	77.4 a	9.0–185
Diarrhea	Absent	217	82.8 a	2.0–176
	Present	30	81.9 a	36.0–185
Neurological signs	Absent	242	82.8 a	2.0–185
	Present	8	72.9 a	5.4–124
Icterus	Absent	218	82.8 a	2.0–131
	Present	31	79.2 a	19.8–185
Admission	Not admitted	139	82.8 a	57.6–131
	Admitted	111	81.0 a	2.0–185
Total		250	83.0	2.0–185

[a] Some data are missing where owners did not know all the answers to the questionnaire. Medians for categories of a variable with different lower-case letters differ significantly ($P < .05$, Kruskal-Wallis one-way ANOVA on ranks).

clinical signs of hypoglycemia in this study population is beyond the scope of this report, it must be noted that a diagnosis of hypoglycemia on the basis of clinical signs poses obvious difficulties in babesiosis because changes in level of consciousness, coma, or seizures can be, and in the past have been, attributed to cerebral babesiosis.[5] Hypoglycemia with associated neurological signs, especially collapse and seizure is thus an important differential diagnosis for cerebral babesiosis.

Although severe anemia was strongly associated with hypoglycemia in the univariate analysis ($P = .0002$), it was not significant in the logistic regression model ($P = .3$), probably because it was also strongly associated with age and mental status. Collapsed dogs were more likely to be severely anemic than alert dogs (odds ratio [OR] = 91, $P < .00001$) and dogs <6 months old were more likely to be severely anemic than dogs >1 year old (OR = 7, $P = .0009$).

The association between severe anemia and hypoglycemia can be explained in the 1st instance by the effects of hypoxia on glycolysis, in that vastly more glucose is consumed during anaerobic glycolysis to produce the same ATP yield. The severity of anemia might also be related to the severity of the disease process and the inflammatory response, which can lead to hypermetabolism and excessive glucose consumption. Severe injury or infection is associated with enhanced cellular uptake of glucose.[51,52] During the inflammatory response, alterations in glucose and fat metabolism occur: the rate of gluconeogenesis increases, as do the rates of lactate and pyruvate formation. Glucose recycling from lactate and alanine accounts for much of the increase in glucose production during stress. Although stress is typically associated with increased gluconeogenesis, there is evidence that septic stress is distinguished by a biphasic response. Lethal models of sepsis in animals demonstrate an initial phase of hyperglycemia during which gluconeogenesis is increased, followed by a subsequent phase during which glucose production is suppressed and hypoglycemia occurs.[15]

The finding that youth was a risk factor for hypoglycemia was consistent with previous reports in humans and dogs. Hypoglycemia is an important and common complication in children with malaria.[9,12] Some studies in dogs have shown that puppies have lower blood glucose concentrations than adults.[53,54] Hypoglycemia in puppies is well documented, with an increased incidence seen in the toy breeds.[39,55] Although the predisposition of toy breeds to hy-

Table 3. Univariable screening of putative risk factors for hypoglycemia in canine babesiosis.

Variable	Category	Hypoglycemia		OR[a]	95% CI	P[b]
		Present	Absent			
Age	<6 months	10	39	3.03	1.22–7.55	.02
	6–11 months	1	46	0.26	0.03–2.03	.31
	≥12 months	12	142	1[c]		
Hematocrit	<10	12	31	12.2	2.57–57.9	.0002
	10–19	8	117	2.15	0.44–10.5	.50
	20–39	2	63	1[c]		
	≥40	1	14	2.25	0.19–26.6	.47
Breed	Small	2	26	0.86	0.18–4.11	1.00
	Medium	10	78	1.43	0.58–3.53	.49
	Large	11	123	1[c]		
Sex	Male	13	118	1.20	0.51–2.85	.83
	Female	10	109	1[c]		
Pregnancy status	Nonpregnant	10	100	1[c]		
	Pregnant	0	9	0	0–∞	1.00
Mental status	Alert	1	79	1[c]		
	Depressed	5	113	3.50	0.40–30.5	.40
	Collapsed	17	35	38.4	4.91–300	<.00001
Time since last meal	<1 day	10	125	1[c]		
	1–3 days	9	78	1.44	0.56–3.71	.47
	≥4 days	2	24	1.04	0.21–5.06	1.00
Vomiting	Absent	16	196	1[c]		
	Present	7	28	3.06	1.16–8.10	.03
Diarrhea	Absent	19	198	1[c]		
	Present	3	27	1.16	0.32–4.17	.74
Neurological signs	Absent	21	221	1[c]		
	Present	2	6	3.51	0.67–18.5	.17
Icterus	Absent	15	203	1[c]		
	Present	8	23	4.71	1.80–12.3	.003
Total		23	227			

[a] Odds ratio relative to reference category.
[b] *P* value, Fisher exact test.
[c] Reference category.

poglycemia is well documented,[39,41,42] there was no association between breed and hypoglycemia in this study.

Hypoglycemia was associated with icterus in this study, although it was not significant in the logistic regression model. Both icterus and hypoglycemia have been identified as indicators of life-threatening malaria.[23] Hepatic glycogenolysis is the primary source of glucose during short periods of fasting. After 24 hours of fasting, hepatic glycogen stores are depleted and gluconeogenesis then plays a greater role in the maintenance of euglycemia.[46,56] In patients that are icteric, these pathways might not function adequately.

The presence of vomiting was significant in the univariate analysis, but not in the logistic regression model. Unfortunately, this is a vague clinical sign with many potential

Table 4. Multiple logistic regression analysis of putative risk factors for hypoglycemia in canine babesiosis.

Factor	Category	β	OR[a]	95% CI	P
Age	<6 months	1.029	2.80	0.81–9.72	.10
	6–11 months	−1.140	0.32	0.04–2.91	.31
	≥12 months	0	1		
Hematocrit	<10	0.974	2.65	0.41–17.3	.31
	10–19	−0.123	0.88	0.14–5.52	.90
	20–39	0	1		
	≥40	0.491	1.63	0.11–24.3	.72
Mental status	Alert	0	1		
	Depressed	0.828	2.29	0.24–21.5	.47
	Collapsed	2.881	17.8	1.86–171	.013
Vomiting	Present	0.422	1.53	0.46–5.07	.49
Neurological signs	Present	−0.543	0.58	0.08–4.46	.60
Icterus	Present	0.342	1.41	0.40–4.99	.60

[a] Odds ratio.

causes and consequences. It could be that patients that are vomiting are less likely to eat and therefore have depleted glucose stores.

The absence of hypoglycemia in the 9 pregnant bitches differs from human malaria, in which pregnancy is an important risk factor.[9,12] However, this result could be a function of the small number of pregnant bitches included in this study.

Hypoglycemia is a common complication of virulent canine babesiosis. Collapsed state and youth were the factors most strongly associated with hypoglycemia, whereas severe anemia, vomiting, and icterus were also risk factors. Hypoglycemia might previously have been undiagnosed and untreated because coma, collapse, and other neurological signs could be misinterpreted as cerebral babesiosis.

Footnotes

[a] Jacobson LJ. Recently described complications of canine babesiosis. Proceedings of SAVA Congress, Durban, South Africa, 2000 (abstract).

[b] Rapidiff stain, CA Milsch, P.O. Box 943, Krugersdorp, 1730, South Africa

[c] Vacutainer System, BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK

[d] Technicon RA 1000 system, Miles Inc, Diagnostics Division, Tarrytown, NY

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