Systemic inflammatory response syndrome and multiple-organ damage/dysfunction in complicated canine babesiosis

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ABSTRACT

This study was designed to document the systemic inflammatory response syndrome (SIRS) and multiple-organ dysfunction syndrome (MODS) in dogs with complicated babesiosis, and to assess their impact on outcome. Ninety-one cases were evaluated retrospectively for SIRS and 56 for MODS. The liver, kidneys, lungs, central nervous system and musculature were assessed. Eighty-seven percent of cases were SIRS-positive. Fifty-two percent of the cases assessed for organ damage had single-organ damage and 48 % had MODS. Outcome was not significantly affected by either SIRS or MODS, but involvement of specific organs had a profound effect. Central nervous system involvement resulted in a 57 times greater chance of death and renal involvement in a 5-fold increased risk compared to all other complications. Lung involvement could not be statistically evaluated owing to co-linearity with other organs, but was associated with high mortality. Liver and muscle damage were common, but did not significantly affect outcome. There are many similarities between the observations in this study and previous human and animal studies in related fields, lending additional support to the body of evidence for shared underlying pathophysiological mechanisms in systemic inflammatory states.

Key words: *Babesia canis,* babesiosis, canine, MODS, multiple-organ dysfunction syndrome, multiple-organ failure, SIRS, systemic inflammatory response syndrome.

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INTRODUCTION

Clinically, canine babesiosis due to *Babesia canis* infection manifests with a wide variety of signs. Haemolytic anaemia combined with fever, lethargy, waterhammer pulse and splenomegaly are the hallmarks of the disease[15,19,21]. However, many 'atypical' signs, or complications[15], can occur. These include acute renal failure, hepatopathy, immune-mediated haemolytic anaemia, pulmonary oedema, rhabdomyolysis and cerebral signs[2,5,15]. The variety of signs and the variable severity of the disease, ranging from relatively mild to peracutely fatal, are characteristic of the South African form of canine babesiosis[15,21]. In order to better define the different forms of canine babesiosis, various classification models have been proposed[15,25]. The most recent divides the disease into complicated and uncomplicated forms. Uncomplicated babesiosis is defined as a clinical syndrome mainly attributable to haemolytic anaemia[15]. Complicated babesiosis covers manifestations that cannot be directly explained by haemolysis, but appear to be the result of the host inflammatory response[15]. Severe and life-threatening complications of babesiosis may or may not be associated with severe haemolytic anaemia, and are frequently associated with a poorer prognosis than severe anaemia alone[15]. The presence of these complications, and their erratic relationship with anaemia, prompted the hypothesis that the pathophysiological mechanisms involved are likely to be similar to those seen in other inflammatory conditions, such as human malaria and canine endotoxaemia[15,19,20,28].

In 1991, the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine took place in order to refine and unify definitions used in the medical literature to document mechanisms resulting in systemic inflammatory states[3]. The term systemic inflammatory response syndrome (SIRS) was introduced to describe a massive inflammatory response to an insult, thus creating a mechanism to describe systemic inflammation in both the presence and absence of infection[3]. Non-infectious causes of SIRS include conditions such as pancreatitis, trauma and heat-stroke[3]. The human model for classifying SIRS has been adopted in veterinary medicine, with[13,14] and without[27] modification. The Consensus Conference also gave definitions for the multiple-organ dysfunction syndrome (MODS) and divided it into primary and secondary MODS[3]. Primary MODS is a direct result of an insult, occurs early and can easily be attributed to the insult, while secondary MODS develops as a result of the host inflammatory response, following a lag phase[3]. The number of affected organs in multiple-organ failure in humans is correlated with mortality. Therefore it was suggested that this might also be the case in dogs with complicated canine babesiosis.

This retrospective study was designed 1) to document whether SIRS and MODS occur in complicated canine babesiosis and 2) to establish whether the presence of SIRS and MODS influences outcome.

MATERIALS AND METHODS

Case records of dogs admitted to the Onderstepoort Veterinary Academic Hospital with babesiosis between 1993 and 1998 were retrospectively studied. Animals were considered for inclusion if: 1) *Babesia canis* parasites had been detected on peripheral thin blood film examination; 2) the dog had been admitted to intensive care; and 3) complicated babesiosis had been detected and recorded. If the clinical status of the dog made immediate admission to the hospital necessary, blood samples had to have been collected before therapy was initiated. In dogs that had been treated for uncomplicated disease and were later admitted owing to delayed onset complications, samples had to have been collected during the first day of hospitalisation. Complications included hepatopathy, acute renal insufficiency, pulmonary oedema, haemoconcentration (so-called 'red biliary'), cerebral babesiosis and acidaemia/acidosis.

The records of animals that fitted the

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selection criteria were scrutinised for the presence of SIRS, using a classification system adapted from Hauptman *et al.*[14]. To be considered SIRS-positive, patients had to have:

- White cell count <6000/mm^3 or >16 000/mm^3, and/or >3 % band cells, *plus* at least 1 of the following:
  - – rectal temperature <38.1 or >39.2 °C; *or*
  - – heart rate >120 beats per minute; *or*
  - – respiratory rate >20 breaths per minute.

Records were then assessed for evidence of organ damage/dysfunction. The liver, muscle, kidneys, lungs and central nervous system (CNS) were evaluated, based on physical findings, radiographic evaluation, serum chemistry evaluation and arterial blood-gas determination. Where necessary, chemical analysis was performed retrospectively on samples stored at –20 °C. Because serum of dogs with complicated babesiosis is frequently heavily discoloured by bilirubin and/or haemoglobin, all samples were visually appraised by the same experienced laboratory technologist and scored on a scale of 1–6 (1 being clear and 6 indicating severe discolouration). Patients with samples that scored 3 or higher, and those for which there was insufficient stored sample volume for the necessary analyses, were excluded from the MODS analysis. Table 1 shows cut-off points for evaluation of organ damage/dysfunction. Organs were assessed as follows:

- Liver damage was assessed using alkaline phosphatase (ALP), alanine aminotransferase (ALT) and glutamate dehydrogenase (GLDH). Fasting bile acids were determined as a measure of hepatic function. Liver damage was defined as a greater than 2-fold increase in an enzyme. Bile acids had to be elevated (>30 µmol/ℓ) in concert with at least 1 abnormal enzyme level because of the cyclic nature of their release[6]. Bilirubin was not included because it was not considered sensitive enough for hepatic damage in a haemolytic disease.
- Serum creatine kinase (CK) levels higher than 5 times top normal (>300 µmol/ℓ) were considered positive for muscle damage. To determine whether the route of the antibabesial drug used caused bias, CK results for animals treated with trypan blue (which is given intravenously) were compared with those treated with diminazene aceturate (given intramuscularly).
- Renal involvement was defined as serum creatinine >150 µmol/ℓ in the absence of clinical dehydration.
- Pulmonary involvement was diagnosed if any 1 of the following criteria was met: 1) arterial oxygen partial pressure (PaO_2) <60 mm Hg; 2) difference between alveolar oxygen partial pressure and arterial oxygen partial pressure (A-a gradient) >15 mm Hg while breathing room air; 3) convincing radiographic evidence of pulmonary oedema; 4) records of a frothy nasal/oral discharge (usually agonal); 5) necropsy confirmation of lung oedema.
- The CNS was evaluated based on clinical records. Dogs showing neurological signs such as seizures, thrashing with excessive vocalisation, cranial nerve deficits and opisthotonus, or altered states of consciousness, were regarded as having cerebral babesiosis. Because of the potential effect of severe anaemia on behaviour and levels of consciousness, patients with haematocrits below 15 % were not considered to suffer from CNS damage unless specific signs, such as seizures or nystagmus, were present.

The Mann-Whitney rank sum test was used to compare CK levels between animals treated with trypan blue and diminazene aceturate. The Fisher exact test was used to evaluate the effect of SIRS and MODS on outcome. Statistical evaluation of possible correlation between single parameters used to assess SIRS and outcome was carried out using the Chi-square test.

RESULTS

Ninety-one cases fulfilled the selection criteria for complicated canine babesiosis and were included in the study. Of 23 different breeds, the most frequently represented were Staffordshire terriers (n = 13), bull terriers (n = 11), German shepherd dogs (n = 11) and boerboels (n = 7). There were 58 males and 25 females (in 8 cases sex was not specified). The age range varied from 2 months to 10 years, with a median of 2.9 years. In 9 cases, outcome was not recorded. These were excluded for the purposes of outcome analysis. Forty-four of the remaining 84 dogs survived, 32 died and 6 were euthanased due to a hopeless prognosis. The mortality rate was thus 45 %. Eighteen dogs died of respiratory failure, 9 of CNS dysfunction and 5 of renal shutdown. The reasons for euthanasia were non-responsive renal shutdown in 3, deterioration of CNS signs in 2, and a combination of hepatopathy and non-responsive renal shutdown in 1. Following assessment of serum quality, 24 cases were excluded from the MODS analysis owing to massive haemoglobinaemia and 8 owing to lipaemia. Sample volumes were insufficient in 3 cases. Thus, out of the 91 cases 56 remained for the biochemical

Table 1: **Parameters and cut-off points for organ damage/dysfunction. Where multiple criteria are present, only 1 had to be abnormal for the organ to be considered positive.**

Organ (system)/parameter	Cut-off values
Liver	
Alanine aminotransferase (ALT)	>80 U/ℓ, 25°C
Alkaline phosphatase (ALP)	>380 U/ℓ, 25°C
Glutamate dehydrogenase (GLDH)	>16 U/ℓ, 25°C
Bile acids	>30 µmol/ℓ, 25°C
Kidneys	
Creatinine	>150 µmol/ℓ, 25°C
Muscle system	
Creatine kinase	>300 U/ℓ, 25°C
Lungs	
Arterial oxygen partial pressure (PaO_2)	
A-a gradient	<60 mm Hg
	>15 mm Hg
Radiology/clinical examination/necropsy	Convincing signs of pulmonary oedema
CNS	
Clinical examination	Presence of seizures, coma or abnormal behaviour

A-a gradient = difference between alveolar oxygen partial pressure and arterial oxygen partial pressure.

part of the study for the evaluation of organ damage.

There was no significant difference in CK levels between dogs treated with trypan blue or diminazene aceturate, excluding the possibility that intramuscular injections of diminazene resulted in bias or caused false-positive results for muscle damage.

Of the 91 cases included in the initial assessment, 79 (87 %) were positive for SIRS. Eight dogs had white cell counts below 6000/mm^3 whereas in 48 dogs they were higher than 16 000/mm^3. In 51 cases, there were more than 3 % band cells. Only 4 dogs had respiratory rates below the cutoff value of 20 breaths/minute. Heart rates of 41 dogs exceeded 120 beats/minute. Body temperature was below 38.1 °C in 24 dogs and exceeded 39.2 °C in 43 dogs.

Of the 56 cases analysed for organ damage/dysfunction, 29 (52 %) had single-organ involvement. The remaining 27 (48 %) had MODS (Fig. 1). In the 29 cases with single-organ involvement, the liver was most commonly involved, followed by kidneys, lungs, CNS and muscle (Fig. 2). Thirteen dogs had 2 organs involved. As shown in Fig. 3, the most common were the liver, lungs and muscle. The organ combinations were liver/lungs (4 cases; 31 %), liver/kidneys (3 cases; 23 %), liver/muscle (2 cases; 15 %), muscle/kidney (2 cases; 15 %), muscle/lungs (1 case; 8 %) and muscle/CNS (1 case; 8 %). Twelve dogs had 3 organs involved, the most common being liver and muscle (Fig. 4). The organ combinations were liver/muscle/kidney in 4 cases (33 %), liver/muscle/lungs in 3 (25 %), liver/kidneys/lungs in 2 (17 %), liver/muscle/CNS in 2 (17 %), and muscle/kidneys/lungs in 1 (8 %). Only 2 dogs had 4 organs involved. Both had involvement of the muscle, kidney and lungs while the 4th organ was liver or CNS (1 each).

Of the 56 cases with demonstrable organ damage, 7 were SIRS negative. Of these, 4 had single-organ involvement and the remaining 3 had multiple-organ involvement. Of these 7 SIRS-negative cases, 2 died.

The presence of SIRS had no statistically significant impact on outcome. None of the individual parameters used to assess SIRS had a statistically significant association with outcome. Outcome was also not affected by whether 1 or multiple organs showed evidence of damage. However, outcome was significantly affected by the specific organ involved. Dogs with CNS involvement had a 57 times greater chance of dying than those with any other organ damage. The presence of renal involvement resulted in a 5-fold risk of death. This indicates that liver or muscle damage did not affect the outcome. The effect of lung damage alone on outcome could not be assessed because it showed a consistent co-linearity with CNS and/or kidney damage. However, it is likely that lung damage is associated with a higher risk of death, considering that more than half of the dogs that died succumbed to respiratory failure.

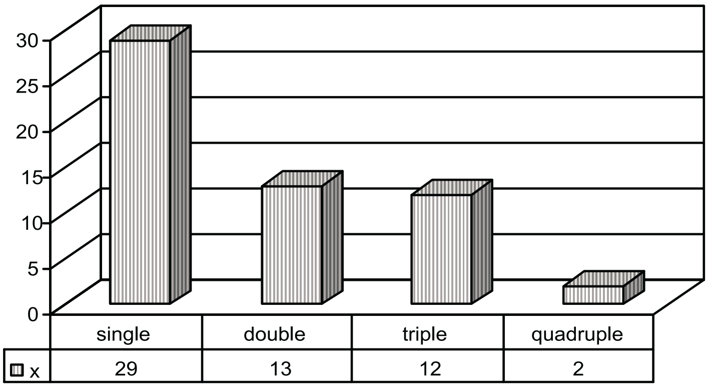

Fig. 1: **Number of affected organs in 56 dogs with complicated babesiosis.**

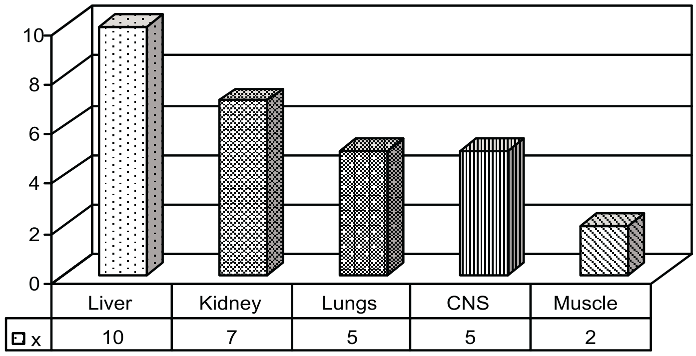

Fig. 2: **Distribution of organ involvement in 29 dogs with complicated babesiosis and single-organ damage; x represents the number of dogs in which that organ was involved.**

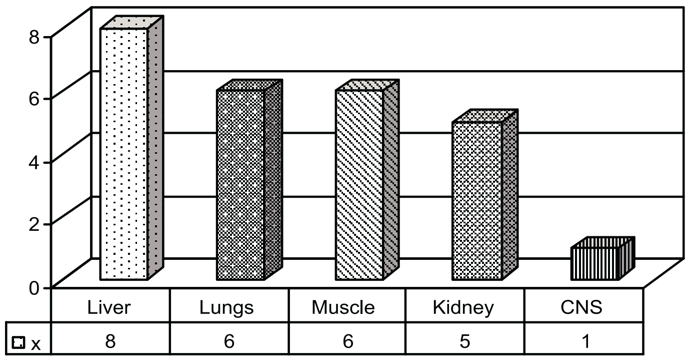

Fig. 3: **Distribution of organ involvement in 13 dogs with complicated babesiosis and double-organ damage; x represents the number of patients in which that organ was involved.**

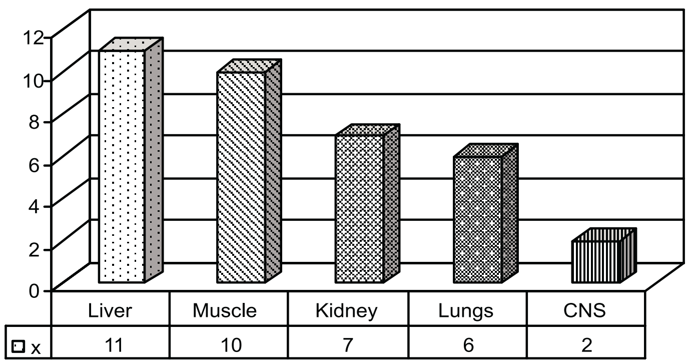

Fig. 4: **Distribution of organ involvement in 12 dogs with complicated babesiosis and triple-organ damage; x represents the number of patients in which that organ was involved.**

DISCUSSION

While the existence of SIRS and the importance of the definition for describing the mechanisms leading to systemic inflammation and MODS have not been disputed, the criteria for defining SIRS have been criticised[22,26,32]. The cut-off values for the clinical parameters are a major issue in human medicine. In the opinion of some, these have been set too widely, with the result that the definition is sensitive but not specific[9,12,22]. Another criticism is that, while SIRS might well identify patients with systemic inflammatory disease, it appears to have little value in distinguishing life-threatening from non-life-threatening conditions, or in predicting outcome[4]. The definition of human SIRS appears to have found its way into veterinary medicine with little critical analysis and with limited attempts to convert the clinical cut-off values into cut-offs suitable for dogs[13,14,27]. This further reduces the usefulness of the definition, particularly since physiological values for temperature, heart rate and respiratory rate show substantial variation in dogs according to size and age[16]. SIRS criteria for veterinary medicine rely on the basic 'two out of four criteria' system presented in the human model[13,14,27].

To avoid proposing an untested model for canine SIRS, a modified version of the classification presented by Hauptman *et al.*[14] was used. Using this classification, 87 % of our cases were classified as SIRS-positive. This was lower than anticipated, as all these animals were suffering from a severe systemic illness characterised by fever and organ damage. Of the 7 SIRS-negative cases with organ damage, 3 had multiple-organ damage and 2 died. These findings indicate weaknesses in the model. Indeed, one might question the clinical benefits of accurately defining SIRS at all. Would the mere knowledge that a patient fits the criteria for SIRS, even if a perfect model could be established, contribute to improved therapy or prediction of outcome? This is doubtful, since it would not provide much information that is not known already. If SIRS is to be clinically useful, prospective studies of large numbers of patients should be conducted to create a more sensitive and specific definition, in terms of both cut-off values and parameters used, and this would need to be linked with outcome and success of interventions. The main argument in favour of the current SIRS definition is that it provides a method, albeit imperfect, of classifying patients for clinical research purposes.

The Consensus Conference discussed the question of whether 'failure' or 'dysfunction' would be more appropriate for classifying organ involvement associated with SIRS[3], and concluded that the term 'failure' was too rigid, and that 'dysfunction' was preferable, since it implies that organ function is not capable of maintaining homeostasis[3]. Owing to the retrospective character of the current study and the fact that for some of the organs studied, our data could only assess damage, rather than dysfunction, we decided to use either the term 'organ damage' (for example, liver enzymes) or 'dysfunction' (for example, cerebral signs) as appropriate.

In multiple-organ failure in humans, the cardiovascular system, gastrointestinal tract and haematological system are often described in addition to the organ systems considered in the current study[11,23]. Documentation of these systems would have been interesting but was impossible owing to the retrospective nature of the study. There seems to be a specific pattern of the sequence of multiple-organ damage in humans. The lungs usually show evidence of damage first, followed by the liver and the kidneys[8,23]. This pattern seems to be characteristic only for adults as paediatric studies describe the kidneys and the microvascular system as the first to show damage[1].

The finding that more than half of our patients only demonstrated single-organ damage/dysfunction was surprising. As patients suffering from complicated babesiosis are generally severely ill, a higher prevalence of multiple-organ damage was expected. One reason for these results could be that secondary organ damage occurs only after a distinct lag phase following the initial insult[3]. In critically-ill humans, a prolonged stay in the intensive care unit might allow more patients to develop MODS, whereas canine patients would be more likely to recover or die in a shorter period. Possibly some of the dogs developed multiple-organ damage after admission. Delayed-onset acute pancreatitis, for example, has recently been reported as a complication of canine babesiosis[24]. It is also possible that organs or organ systems not assessed in this study were affected. A prospective study with a defined date of insult and a longer period of observation would be required to clarify these points.

Individual organs showed different patterns of involvement as the number of affected organs changed (see Figs 2–4). It is difficult to comment on quadruple organ dysfunction because the numbers were small; this discussion will therefore confine itself to single, double and triple organ involvement. The liver was most frequently represented, in both absolute and proportional terms, in all groups, and the proportion of patients with liver damage climbed steeply as the number of affected organs rose. There are 2 possible explanations. On one hand, the liver plays a central role in metabolism, and is sensitive to hypoxia[30], and liver damage/dysfunction is common in inflammatory states[7,29]. A methodological bias could also explain the results, however, as the presence of liver damage was tested using 4 parameters, some of which are elevated in acute but non-severe damage, rather than specifically reflecting dyshomeostasis. The criteria for liver damage were thus sensitive but not specific. The kidneys and lungs were characterised by a moderate rise in frequency of damage as the number of affected organs rose, and showed similar rates of damage. The lungs were almost equally involved in double and triple organ damage, while kidney damage showed a moderate increase in proportion to the number of total organs affected. Muscle damage followed an interesting pattern, representing the lowest percentage of all affected organs in the single-organ failure group but rising steeply to second place in triple organ failure. This indicates that muscle damage is either a late event in MODS, or is a 'bystander' event, accompanying or resulting from damage to other organs. The CNS behaved differently from all other systems, with a low incidence of involvement in all groups, which did not increase as the number of affected organs increased.

The fact that a positive result for SIRS did not increase the risk of death was not surprising, given the nonspecific nature of the definition. More surprising was the fact that the presence of multiple-organ damage did not result in a worse outcome compared with single-organ damage. This contrasts with reports of MODS in different human diseases, where outcome was correlated with the number of organs involved[10,17] One factor contributing to this result was the high impact of CNS dysfunction on outcome, in conjunction with the fact that CNS involvement was found in similar proportions in the single- and multiple-organ groups. Another factor was that liver and muscle, which were prominently represented in double and triple organ dysfunction, had no influence on outcome. The organ-specific odds ratios in studies of multiple-organ failure as well as complicated malaria in humans are consistent with our results, as liver damage was associated with the lowest mortality whereas damage of the CNS or kidneys had the highest odds ratios[11,18].

Taken together, these findings support the hypothesis that complicated canine babesiosis shares a common pathomechanism with other inflammatory diseases such as malaria and canine endotoxaemia[15,19,28]. The importance of CNS and kidney involvement as predictors of outcome in canine babesiosis is consistent with previous studies, which indicated that azotaemia and CNS signs were important factors in a predictive model for the disease[31]. CNS involvement was a particularly poor prognostic sign, while urea and creatinine were the only biochemical markers which differed significantly between survivors and non-survivors[31]. Although ALT was included in the model, it did not have a high weighting, and other liver enzymes considered (ALP, GLDH) were not found useful in determining the prognosis[31]. Indicators of muscle and lung damage were not included[31]. In the current study, although the effect of lung damage on outcome could not be assessed statistically, it was involved in a large proportion of deaths, and would probably have been associated with a high risk for death.

CONCLUSIONS

SIRS and MODS occur frequently in complicated canine babesiosis. The results of this study indicate that the criteria used to identify SIRS in veterinary medicine need revision, as a significant number of dogs with MODS were not recognized as SIRS positive. Outcome was more strongly associated with specific single-organ damage than with evidence of multiple-organ involvement. Specific organ damage associated with poor outcome in this study were the brain, lungs and kidneys. The liver and muscle were frequently damaged but did not appear to impact on outcome. Muscle damage was increasingly evident as multiple organs showed evidence of involvement.

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