The Veterinary Journal 198 (2013) 43–47

Contents lists available at SciVerse ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Prognosis and monitoring of leishmaniasis in dogs: A working group report

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ARTICLE INFO

Article history:
Accepted 3 April 2013

Keywords:
Canine
Leishmania infantum
Prognosis
Monitoring
Working group

ABSTRACT

This review presents the consensus opinion of the Canine Leishmaniasis Working Group on the prognosis and monitoring of leishmaniasis in dogs. While the prognosis for both exposed and infected dogs is considered to be favourable, this changes if infection progresses to overt disease. For clinically affected animals undergoing treatment, the prognosis is dictated by the severity of the signs (and in particular the severity of renal dysfunction) when therapy is initiated; assessing the degree of proteinuria is useful in this context. Approximately 75% of dogs without evidence of renal involvement live for >4 years if adequately treated. Monitoring the response to treatment includes ongoing clinical and clinicopathological assessment, as well as quantifying serological responses and the parasite load in the patient.

Introduction

In 2005, the Canine Leishmaniasis Working Group (CLWG) was established to provide an evidence-based consensus for the diagnosis and treatment of this disease. In the intervening years, this group has published guidelines relating to various aspects of the diagnosis, treatment and prevention of canine leishmaniasis (Castagnaro et al., 2007; Oliva et al., 2008, 2010, 2011; Maroli et al., 2009, 2010; Paltrinieri et al., 2010, 2011). In this review, we report the recommendations of the CLWG on the prognosis and monitoring of canine leishmaniasis, which are based on the available scientific evidence and the consensus opinion of group members.

Prognosis

Prognosis is the prediction of the probable course and outcome of a disease and typically depends on the severity of the disease and its response to treatment. Predicting the outcome of leishmaniasis in dogs can be challenging, given the lack of controlled studies evaluating prognostic factors (Castagnaro et al., 2007). There has been some focus on the usefulness of the 'staging' of leishmaniasis to identify the most effective treatment and anticipate the outcome (Oliva et al., 2008, 2010; Solano-Gallego et al., 2009; Paltrinieri et al., 2011). A complete clinical and laboratory-based assessment of each dog at the time of diagnosis, together with serological responses and parasite detection, are necessary to characterise the severity of disease and to assign the case to a clinical stage (dos-Santos et al., 2008; Reis et al., 2009). Following diagnosis, the patient should be periodically re-evaluated and re-classified in line with disease progression or regression (Solano-Gallego et al., 2009; Oliva et al., 2010; Paltrinieri et al., 2010). Table 1 details the CLWG recommendations regarding the staging of canine leishmaniasis (Oliva et al., 2008; Paltrinieri et al., 2010).

For dogs in stage A (exposed), the prognosis is favourable and any circulating antibodies can be transitory (Castagnaro et al., 2007; Oliva et al., 2008, 2010; Paltrinieri et al., 2010). Approximately 25% of exposed dogs originating from endemic areas can develop spontaneous sero-reversion within a few months, even in the

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http://dx.doi.org/10.1016/j.tvjl.2013.04.001

Table 1
Staging of cases of canine leishmaniasis.

Stage	Definition	Description
A	Exposed	Clinically normal or have signs associated with other diseases. Infection cannot be demonstrated by microscopy, culture or PCR and a specific antibody titre is <4 times the reference value. Such animals live or have lived during >one 'transmission season' in a geographical region where sand flies are endemic
B	Infected	Clinically normal or have signs associated with other diseases. Parasites have been demonstrated by microscopy, culture or PCR and a specific antibody titre is negative or is <4 times the reference value
C	Clinically diseased	Dogs exhibit clinical signs and/or clinicopathological abnormalities associated with leishmaniasis. Infection demonstrated by microscopy, culture or PCR and by seropositivity, irrespective of extent. Given the variable clinical and clinicopathological expression of leishmaniasis, observed signs can differ from those commonly described. Dogs with clinical signs and/or clinicopathological abnormalities associated with leishmaniasis and an antibody titre $\geqslant$ 4 times the laboratory reference value can also be considered clinically diseased even if the parasite cannot be demonstrated
D	Severely clinically diseased	Dogs with: (1) proteinuric nephropathy; (2) severe kidney disease (IRIS stage 3–4); (3) severe ophthalmic disease that can lead to functional loss and/or require immunosuppressive therapy; (4) severe joint disease leading to loss of motor function and/or require immunosuppressive therapy; and (5) severe concomitant disease(s)
E	Unresponsive to treatment (Ea)	Clinically unresponsive to recommended treatment(s)
	Early relapse (Eb)	Clinical relapse soon following cessation of recommended treatment(s)

absence of therapy (Acedo-Sánchez et al., 1998; Otranto et al., 2009). Similarly, for dogs in stage B (infected), the prognosis is favourable if the infection, considered to be persistent in most dogs, does not progress to overt disease (Castagnaro et al., 2007; Oliva et al., 2008, 2010; Paltrinieri et al., 2010). Cytological identification of the parasite on lymph node or bone marrow smears, along with a progressive increase in antibody titre, is a clear indication of progression towards overt disease. While this can occur over a period varying from weeks to years, animals may also remain sub-clinically infected throughout their lives (Baneth et al., 2008).

In the absence of treatment, 30–70% of infected dogs from endemic regions develop clinical disease within 2–3 years of diagnosis (Manna et al., 2006; Oliva et al., 2006; Otranto et al., 2009; Paradies et al., 2010). Currently, there is no single laboratory test, or combination of tests, that can predict if an infected dog will develop overt disease. Dogs of the Podenco Ibicenco breed have a cell-mediated immune response to infection that makes them relatively resistant to infection (Solano-Gallego et al., 2000), while Boxer dogs appear to be highly susceptible (Miranda et al., 2008; Quilez et al., 2012). For dogs with clinical signs in stages C, D and E of disease, the prognosis depends on the severity of any clinicopathological abnormalities presenting when therapy is initiated, the individual response to therapy and, particularly, the severity of any renal damage (Noli and Auxilia, 2005). Kidney function in this context should be assessed according to the recommendations of the International Renal Interest Society (IRIS) for the staging of chronic renal disease in dogs (Elliott and Watson, 2009). The prognostic value of proteinuria should be considered at the end of treatment for canine leishmaniasis (Plevraki et al., 2006), although the prognosis is poor in the majority of severely affected untreated animals (dos-Santos et al., 2008).

The therapeutic protocol can influence prognosis; the information provided below concerning prognosis and monitoring refers to dogs treated with N-methylglucamine antimoniate and allopurinol, currently considered to be the 'drugs of choice' in the treatment of leishmaniasis (Noli and Auxilia, 2005; Oliva et al., 2008, 2010, 2011). The use of a combination of miltefosine and allopurinol as treatment is promising and may possibly turn out to be as effective as giving N-methylglucamine antimoniate and allopurinol (Miró et al., 2009). More than 50% of dogs had relapses after approximately 5 months if treated with marbofloxacin alone (Rougier et al., 2012). However, little data is available on alternative treatment protocols.

The prognosis for dogs with stage C disease varies from 'favourable' to 'guarded' (Torres et al., 2011; Paradies et al., 2012; Rougier et al., 2012), while for those at stages D and Eb, in the absence of severe renal disease (i.e. IRIS stage 1–2; serum creatinine levels <2.1 mg/dL), the prognosis is similar, as long as animals are treated with N-methylglucamine antimoniate and allopurinol (Denerolle and Bourdoiseau, 1999; Torres et al., 2011). However, where severe kidney disease is evident (i.e. IRIS stage 3–4), the prognosis changes from 'guarded' to 'poor' (Koutinas et al., 1999; Plevraki et al., 2006; Planellas et al., 2009). Advanced renal disease is the major cause of death, or the reason for euthanasia, in dogs with leishmaniasis (Mancianti et al., 1988; Ferrer et al., 1995; Slappendel and Ferrer, 1998; Planellas et al., 2009). A proportion of dogs in at IRIS stage 3–4 may have a prolonged survival if treated appropriately and thus the CLWG proposes that treatment of animals at stages C, D and Eb should be attempted, irrespective of IRIS classification.

In a study by Slappendel (1988), only 4/14 dogs with leishmaniasis and azotaemia at the commencement of treatment with meglumine antimoniate survived >1 year. In dogs without renal disease, 75% that were treated survived for >4 years (Slappendel, 1988; Alvar et al., 1994; Slappendel and Teske, 1997; Denerolle and Bourdoiseau, 1999). In most cases, the clinical signs abated with treatment, even though >70% of dogs had recurrence of disease within 2 years (Slappendel, 1988; Alvar et al., 1994; Slappendel and Teske, 1997; Denerolle and Bourdoiseau, 1999). In view of recent improvements in the diagnosis and treatment of leishmaniasis and renal disease, the prognosis for canine leishmaniasis, with or without renal damage, is favourable (Finco et al., 1999; Solano-Gallego et al., 2009; Oliva et al., 2010; Torres et al., 2011). In a study of 23 dogs with normal renal parameters or only mild proteinuria (proteinuria/creatinuria, PU/CU, <1), 90% had amelioration of clinical signs and return their clinicopathological parameters returned to normal within 3 months of treatment with meglumine antimoniate and allopurinol (Torres et al., 2011). Dogs with mild renal disease (IRIS stage 2, with or without proteinuria) exhibited partial improvement in renal function and good survival times following specific therapy (Planellas et al., 2009).

The prognosis for dogs in leishmaniasis stages C, D or Eb and with IRIS stages 1 or 2 depends on the severity of proteinuria and its response to therapy, as well as on the efficacy of treatment (Castagnaro et al., 2007). Animals in IRIS stages 1 or 2, where proteinuria is not reduced by treatment, have a poorer prognosis than dogs with similar staging but higher initial proteinuria that progressively decreases following therapy. Proteinuria generally decreases after 4–6 weeks of combined treatment with meglumine antimoniate and allopurinol, or with allopurinol alone; a more rapid decrease in proteinuria is observed with antimonials compared to treatment with allopurinol alone (Plevraki et al., 2006). Thus, renal function and proteinuria should be re-evaluated in dogs with leishmaniasis after 4–6 weeks of treatment (Elliott and Watson, 2009). Dogs with leishmaniasis at IRIS stages 3 or 4 had a poorer prognosis than those at IRIS stages 1 or 2; progression of renal dysfunction was the most common cause of death in this category of