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General information

Answers to most questions regarding leishmaniosis can be found within the LeishVet guidelines http://www.leishvet.org/fact-sheet/. These were updated in March 2024 and are based on a small number of studies (dogs with primarily moderate to severe disease) and the expert opinion of specialist vets and researchers that live and work in areas where *Leishmania* is endemic). The LeishVet guidelines are also available in several European languages.

Canine leishmaniosis

Canine leishmaniosis is primarily caused by the protozoan parasite *Leishmania infantum*, of which dogs are the major reservoir for infection. Canine leishmaniosis is extremely common in countries surrounding the Mediterranean basin where the primary vector, sand flies of the *Phlebotomus* species, are endemic. Canine leishmaniosis is also common in South America and more recently was seen to spread across the USA and Canada, particularly in the fox hound breed.

In the absence of a sand fly vector, direct transmission can be seen via horizontal (DOI: 10.1136/ vr.105157; DOI: 10.1136/vr.11268), venereal, and vertical routes (DOI: 10.1371/journal.pntd.0007058; DOI: 10.1371/journal.pntd.0001019). Iatrogenic transmission is also possible, via contaminated blood products (DOI: 10.1016/j.vetpar.2005.12.011).

In endemic areas the infection seroprevalence may approach 90% but most dogs have minimal to no clinical signs.

Diagnosing leishmaniosis

What clinical signs are consistent with leishmaniosis?

Leishmaniosis is a chronic disease with a long incubation period – it can be 3 months to 7 years after infection that clinical signs may develop. Manifestation, severity, chronicity, and progression is highly variable. The host immune response plays a large part in determining the outcome of infection; an ineffective cell mediated immune response with a pronounced humoral response is associated with clinical disease. Clinical signs, where present, can include:

- **Cutaneous lesions** (classically exfoliative dermatitis with alopecia and scaling is seen, with ulceration and nodules also common) especially affecting the head and pressure points. With very chronic infection onychogryphosis (abnormal nails) may be seen. Pruritus is often minimal unless there is secondary bacterial infection. (DOI: 10.1111/j.1365-3164.1992.tb00158.x).

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- **Ocular signs *** (including conjunctivitis, dry eye diseases, anterior and posterior uveitis, and glaucoma). (DOI: 10.1046/j.1463-5224.2000.00106.x)
- **Polyarthropathy** (painful, often swollen, joints; resulting in lethargy and lameness)
- **Lymphadenopathy**; splenomegaly

Other clinical signs can include: weight loss & poor body condition; fever; bleeding diatheses (e.g. epistaxis; excessive bleeding after venepuncture); kidney disease-associated signs e.g. polyuria / polydipsia; enteropathies and malabsorptive disease; evidence of mild to moderate bone marrow suppression (pallor; opportunistic infection).

* If there is significant ocular involvement, early referral to a specialist in veterinary ophthalmology should be considered.

What laboratory changes can occur with leishmaniosis?

The following non-specific clinicopathological changes are commonly seen with clinical leishmaniosis:

- Routine haematology: **non-regenerative anaemia** or (less commonly) regenerative anaemia due to immune-mediated haemolysis. Occasionally (typically only mild to moderate) thrombocytopenia or neutropenia.
- Serum biochemistry (fasted): **hyperglobulinaemia**. Hypoalbuminaemia compensatory to hyperglobulinaemia or increased losses. Azotaemia and / or increased liver enzyme activities can occur.
- Urine analysis: proteinuria (urine protein creatinine ratio, UPC ≥0.5).

Even in dogs where leishmaniosis is suspected or confirmed, full haematology (including blood film examination), serum biochemistry, and urinalysis (including UPC) – preferably at an external laboratory – are recommended to stage the disease prior to treatment.

Serum protein electrophoresis is unlikely to alter case management so is not routinely recommended. Similarly, the utility of serological markers of systemic inflammation (e.g. C-reactive protein) is not clear; these remain a focus of investigation.

Testing for concurrent disease

Evaluation of concurrent disease that may either require treatment, or be contributing to some or all clinical signs, should be considered. Concurrent infection with non-endemic pathogens may cause or contribute to presenting signs, increase risk of relapse, and worsen the prognosis. Test selection should be based on the country of import / prior residence. There is significant overlap in both the distribution of and risk factors for infection with *Leishmania* and other arthropod-vectored pathogens, especially *Ehrlichia*, *Anaplasma*, *Babesia*, and *Dirofilaria* (e.g. heartworm).

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We also recommend performing *Brucella canis* serology if there is a history of travel from / within *Brucella* endemic countries (Canine-Brucellosis-Summary.pdf (defra.gov.uk).

In dogs that develop leishmaniosis for the first time many years after likely exposure, presence of an underlying trigger should be considered e.g. recent use of immunosuppressive medication or presence of neoplasia.

How do I diagnose a dog with leishmaniosis?

Confirmation of **active** *Leishmania* infection is based on compatible clinical signs, clinical examination findings, routine clinicopathological test results, serology, cytology and/or histology and/or PCR. Compatible clinical signs, positive serology, and a response to treatment would also support a diagnosis of leishmaniosis in the absence of supportive cytological or PCR results; however, a plan to defer investigation pending response to treatment can result in a missed or delayed diagnosis of concurrent disease.

Subclinical infection is common and demonstrated by seropositivity in the absence of compatible clinical signs or clinicopathological changes.

Serology

The detection of *Leishmania*-specific antibodies in the serum of dogs is very useful in the diagnosis of *Leishmania* infection. Although it can take a few months for dogs to seroconvert (up to 22 months, although median is 5 months) the long incubation period with *Leishmania* means that most sick dogs are likely to have a positive serology result; however, in isolation, a positive serology result only indicates exposure to *Leishmania* (or vaccination) and not clinical disease.

- Qualitative serology – ELISA or lateral-flow
  - Cheap; point-of-care
  - Screening purposes only → positive results should be quantified
  - Some are specific for infection-associated antibodies and can be used in previously vaccinated dogs (e.g. Speed Leish K™, Speed Duo Leish K/Ehrli™, Virbac; SNAP® Leish 4Dx, SNAP® *Leishmania*, IDEXX)
- Quantitative serology – ELISA, such as the one offered by **Langford Vets Diagnostic Laboratories (Acarus)**, or immunofluorescence antibody test (IFAT)
  - Both quantitative ELISA and IFAT are regarded as being suitable for diagnostic and monitoring purposes, although some subjectivity occurs in the interpretation of IFAT titres
  - Necessary when investigating dogs with strongly suspected or known infection
  - May cross-react with vaccinational antibodies

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- Serial monitoring (e.g. for response to treatment or for evidence of relapse) should be performed using the **same quantitative assay** at the **same laboratory** – *results obtained from different laboratories are not comparable*.

Quantitative results should be considered alongside travel history, treatment administered (including vaccination), clinical signs, and other clinicopathological results (see above)

- High antibody levels can strongly support a diagnosis of active disease
- Low antibody levels are not usually indicative of disease, but do not rule it out
- A negative result does not rule out infection or active disease (some dogs do not seroconvert or have delayed seroconversion)

If leishmaniosis is still suspected in a dog with a low or negative serology result: additional diagnostic tests such as cytology / histology and PCR are indicated to help confirm or exclude active *Leishmania* infection, differential diagnoses should be reviewed, and repeat serology performed after 3-6 months.

Direct visualisation (cytology / histopathology)

Finding *Leishmania* organisms on stained smears or sections prepared from fine needle aspirates, impression smears, or biopsies of affected tissues (e.g. bone marrow, lymph node, skin, and joint fluid) confirms infection, although the examiner needs to be experienced in identifying organisms. Organisms can be scarce and only present in certain organs, reducing the sensitivity of this technique. Samples should only be obtained in dogs in which clinical leishmaniosis is suspected due to the presence of consistent clinical signs and / or clinicopathological changes.

Samples showing pathology consistent with *Leishmania* infection e.g. (pyo)granulomatous or lymphoplasmacytic inflammation or lymph node reactive hyperplasia, as well as organisms, are more likely to represent clinically significant *Leishmania* infection.

Polymerase chain reaction (PCR)

Quantitative PCR results should be considered alongside travel and treatment history, clinical signs, and additional clinicopathological test results (including serology). In most dogs, serology is prioritized over PCR for screening, diagnosis, and monitoring purposes.

PCR is a sensitive and specific technique that amplifies any *Leishmania infantum* DNA present in submitted samples. PCRs based on amplifying *Leishmania* kinetoplast DNA (kDNA), such as the real-time quantitative PCR offered by **Langford Vets Diagnostic Laboratories (Acarus)**, are particularly sensitive due to the many thousands of kDNA copies present in each *Leishmania* organism. Quantification of *Leishmania* DNA levels in the sample may assist in diagnosis and treatment monitoring (higher levels consistent with severe disease; *Leishmania* organism

numbers should fall quite quickly with effective treatment; if previously positive, negative PCR results should be obtained before treatment is stopped).

Ideal tissues to submit for PCR are those in which organisms are believed to be present based on clinical examination or cytological / histological results. Otherwise, the sensitivity of detection by PCR appears to be as follows: bone marrow or lymph node aspirates > skin aspirates > conjunctival swabs > buffy coat > whole blood (not serum). So, although blood is often positive by PCR in clinical leishmaniosis, a negative result cannot be used to rule out disease, and in these cases concurrent serology testing is important to determine if clinical *Leishmania* disease is likely where there are consistent clinical signs and / or clinicopathological changes.

PCR can be positive in dogs that are *Leishmania*-infected, but which do not have active disease. PCR may also be positive in early disease prior to seroconversion.

Staging of dogs with leishmaniosis

Staging is recommended to guide treatment, monitoring, and prognosis. The following has been modified from the LeishVet guidelines. NB: all dogs infected with *Leishmania* are considered to have chronic kidney disease (CKD) of International Renal Interest Society (IRIS) stage 1 or greater (http://www.iris-kidney.com/) regardless of physical, diagnostic imaging, or laboratory findings.

Stage	Clinical signs	Routine laboratory change	Serology
1 – Mild	Mild / localised skin lesions or lymphadenopathy	None	Negative / low positive
2 – Moderate	Moderate-severe / generalised skin lesions or lymphadenopathy. Mild systemic signs	Classical: mild anaemia, hyperglobulinaemia *but* non-azotaemic Substage: a) Non-proteinuric b) Mild proteinuria (UPC 0.5-1)	Usually positive
3 – Severe	As per stage 1 or 2 *plus* immune-complex disease (e.g. uveitis, polyarthritis, glomerulonephritis)	As per stage 2 ± CKD IRIS stage 1 with proteinuria (UPC 1-5) ± CKD IRIS stage 2 with UPC <5	Usually high
4 – Very severe	As per stage 3 ± Thromboembolism ± Nephrotic syndrome ± Uraemia	As per stage 2 or 3 ± Marked proteinuria (UPC >5) ± CKD IRIS stage 3 or stage 4	Usually high

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Treatment

When to treat

Treatment is indicated if a dog has **active *Leishmania* infection (moderate to very severe disease) *with* associated clinical signs or clinicopathological change of concern** (e.g. moderate-severe cytopenias; proteinuria; moderate-severe hyperglobulinaemia).

The need to treat *Leishmania*-infected dogs with mild disease is equivocal

- Minimal evidence base
- Some might self-resolve without treatment
- May respond to monotherapy, short-duration dual therapy, and / or immune-support medication (see below)

Treatment of *Leishmania*-infected dogs with very high or rapidly increasing antibody titres *without* clinical signs (following very careful physical examination) or clinicopathological change is controversial (see relevant section at the end).

Treatment protocols

Allopurinol monotherapy is not recommended, unless for very focal cutaneous disease with no evidence of systemic disease (controversial). Allopurinol monotherapy is associated with a slower clinical response, increased risk of treatment failure, and increased risk of drug resistance – but if owner finances are very limited it could be considered (with informed consent). Meglumine antimoniate monotherapy is also associated with high risk of treatment failure.

Treatment with allopurinol *plus* either meglumine antimoniate or miltefosine is recommended. The preference to use meglumine antimoniate as an induction agent, despite the adverse effects and need to inject, is because it is associated with reduced frequency of relapse (cf. miltefosine; DOI: 10.1186/s13071-015-0896-0) in a randomised clinical trial; however, the number of dogs in each arm of this clinical trial was small. Miltefosine is easier to administer (oral liquid), is significantly cheaper (once sundries and monitoring are considered), and is associated with fewer adverse effects. In the short term (<7 months) the treatments are equivalent (DOI: 10.1111/j.1365-3164.2009.00824.x). In a large (n=173) long term follow-up cohort study, miltefosine *plus* allopurinol (2-12 months) resulted in clinical improvement in nearly all treated dogs (98%), and only 17% relapsed (DOI: 10.3390/pathogens12070864). In a smaller (n=57) clinical trial of dogs that received meglumine *plus* allopurinol (12 months) only 21% relapsed within the 2-year follow-up (*personal communication*).

- Induction phase:
  - Meglumine antimoniate or miltefosine *plus* allopurinol (treatment with allopurinol can start pending receipt of the meglumine antimoniate or miltefosine)

- Typically for 4 weeks
- Assess response at end of phase (extension of the induction phase may be considered in selected cases with inadequate response)

➢ Maintenance phase
- Allopurinol continued
- Typically for a further 5-11 months in the first instance if well tolerated
- Assess progress and for side effects every 3-4 months during treatment

Drug	Dose	Adverse effects
Meglumine antimoniate (Glucantime®; 300mg/mL)	100 mg/kg SC once daily (ideally given divided twice daily)*	Pain, swelling at injection site – try and use different injection sites daily and massage well afterwards (sometimes anti-inflammatory prednisolone is required for 3-5 days if severe reactions). Fever, loss of appetite and diarrhoea are occasionally reported. Transient increase in liver enzymes sometimes seen. Transient acute kidney injury (tubular) is rare.
Miltefosine (Milteforan™; 20mg/mL)	2mg/kg PO once daily with food	Vomiting, diarrhoea (usually occurs within 5-7 days of starting treatment and is self-limiting over 1-2 days, so no treatment usually required)
Allopurinol (generic)	10 mg/kg PO twice daily	Xanthine uroliths – can monitor using ultrasound. Although xanthine crystalluria is common, urolithiasis seems to be relatively uncommon. If occurs then need dietary management and/or reduce dose of allopurinol to 5 mg/kg BID or 2.5 mg/kg BID, ensuring control of *Leishmania* remains.

*Consider starting at 50mg/kg divided daily, and re-assess urea, creatinine and UPC after 3 days – especially if there is concern regarding kidney function.

Additional treatment considerations

Supportive care may be required e.g. antibiotics for secondary bacterial pyoderma, treatment for *Malassezia* if present, intravenous fluid therapy if dehydrated, pain relief if lame due to polyarthropathy (e.g. paracetamol; opioids).

Topical or systemic corticosteroids may be necessary when there are clinical signs associated with inflammation secondary to deposition of immunocomplexes (e.g. uveitis, glomerulonephritis, polyarthritis). Where used systemically, usually a short course (7-15 days) of prednisone is desirable, starting at 0.5-1 mg/kg/day, tapered to stop.

Diet – see below under Dietary Management.

In dogs that are moderate (UPC 1-5) to markedly (UPC >5) proteinuric, in addition to further characterisation of any associated complicating factors (e.g. hypertension; hypercoagulability) specific treatment is often necessary. The IRIS consensus recommendations for standard therapy

of glomerular disease in dogs should be followed, alongside therapy for Leishmania (https://onlinelibrary.wiley.com/doi/10.1111/jvim.12230) should be followed.

Alternative treatment options

Various alternative (typically lower) doses and dosing schedules for allopurinol are anecdotally used in the long-term management of leishmaniosis. They are often used to either reduce costs or reduce the risk of urolithiasis. There are little to no data to support these schedules as being equivalent or superior to the current widely recommended one. Subtherapeutic or pulse treatments are also more likely to select for drug resistance. Other, less favoured, drugs with anti-*Leishmania* activity include amphotericin B, metronidazole (in combination with spiramycin), and marbofloxacin. Further studies are required to justify the use of these medications.

In clinically well or minimally affected infected dogs **immune-support medication** can be considered (DOI: 10.1016/j.rvsc.2019.06.009). Domperidone (DOI: 10.1590/0074-02760180301) and / or Impromune® (DOI: 10.3390/microorganisms9122601) can be used alongside or in place of standard treatment, individually, or in combination. We most frequently use domperidone in dogs that have failed standard therapy, in clinically healthy dogs that frequently relapse to try to reduce the risk of relapse (DOI: 10.1186/s13071-023-05903-0), and dogs that have very mild disease in place of anti-*Leishmania* treatment. Impromune (a combination of nucleotides and other immunostimulatory compounds) can also be considered as an alternative to allopurinol where side effects preclude its continued use.

- Domperidone – 0.5 mg/kg once daily for 28 days every 4 months
- Impromune® – is based on weight category (½ tablet if ≤10kg; 1 tablet if 11-25kg; 2 tablets if ≥26kg or more) and given daily ongoing. It is more expensive than domperidone.

Vaccination has not been shown to be effective in the face of clinical signs, and it can interfere with serological testing.

Sourcing medication

Obtaining meglumine antimoniate or miltefosine

Both meglumine antimoniate (Glucantime®; 1.5g/5mL; packets of 5 ampoules of 5mL; Sanofi Aventis, France / Spain) and miltefosine (Milteforan™; 20mg/ml; 30mL or 60mL bottles; Virbac, France / Spain) need a special import certificate (SIC) for the individual patient prior to ordering. SICs are readily available, free-of-charge, from the VMD website (https://www.vmd.defra.gov.uk/sis/default.aspx). Select the 'Apply for Special Import Certificate (To import a veterinary medicinal product authorised within the EU)' option, which will then require you to enter your RCVS membership number to continue. The first time you do this, you will need to register yourself and your practice.

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Even after obtaining a SIC, it is not usually possible to source either medication from regular veterinary wholesalers. Milteforan (as a 60mL bottle) is available directly from the manufacturer Virbac. Merlin vet exports (www.merlinvet.co.uk) are also able to supply both Milteforan (as 30mL or 60mL bottles) and Glucantime. Other importers (e.g. Henry Schein www.henryschein.co.uk) are available. These items are invariably non-refundable.

Obtaining allopurinol

Generic allopurinol tablets (100mg; 300 mg; POM) can usually be sourced from regular veterinary wholesalers or human pharmacies.

Obtaining domperidone

A liquid formulation of domperidone (Leisguard®, Ecuphar, Spain; 5mg/mL) is licensed for use in dogs in Continental Europe and can be imported via the same route as meglumine antimoniate and miltefosine. However, generic domperidone tablets (10mg; POM) can usually be sourced from regular veterinary wholesalers or human pharmacies.

Obtaining Impromune

Impromune® (Bioiberica) is considered a nutritional supplement. Consequently, it can be sourced directly by owners (online) without prescription.

Management of urolithiasis risk

The biggest risk of chronic allopurinol use is xanthine urolithiasis leading to urinary tract obstruction (urethral or ureteral). Urolithiasis can be painful, life-threatening, and expensive to manage (e.g. surgery may be necessary).

Xanthine is a natural by-product of purine breakdown, the pathway beyond which is inhibited by allopurinol, resulting in xanthine accumulation. Presence of concentrated urine and feeding a high purine diet increase the risk of xanthine crystalluria and, consequently, xanthine urolithiasis. In dogs given allopurinol, efforts should be made to promote dilute urine (reduces crystal formation and encourages bladder emptying) and reduce xanthine production.

Dietary management in leishmaniosis

From the start of allopurinol treatment, **dogs should be encouraged to increase their water intake** by offering wet food / soaked kibble and having free access to fresh water.

Dogs should be fed a low-purine diet during allopurinol treatment. There is a diet specifically optimised for the adjunctive management of dogs with leishmaniosis without significant kidney disease: Advance Veterinary Diets: Urinary Low Purine (soya and egg-based). Royal Canin Dalmatian (vegetable protein and egg-based), Royal Canin Hypoallergenic Dog (soya-based), and Purina ProPlan Canine HA Hypoallergenic (soya-based) are also formulated to have lower

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levels of purines cf. standard dog food, while maintaining normal protein levels. Commercial vegetarian and vegan diets are likely to contain relatively low levels of purines.

In adult dogs where xanthine stones have formed, more extreme low protein, low purine diets that should be considered include Hill's U/D (canned and dry) and Royal Canine Urinary U/C Low Purine. When these diets are fed, close monitoring of serum protein levels is recommended, especially if there is proteinuria. These diets, especially Hill's U/D are not suitable for long term use.

In dogs with chronic kidney disease, feeding of a kidney support diet (restricted protein; low phosphorus) is usually prioritized. Royal Canin Multifunction Renal + Hypoallergenic for dogs (soya-based) offers both support for the kidneys and a reduced purine formulation.

Some of these diets are only available online or via vets. Meat-based treats should be avoided, and plant-based treats should be used as an alternative where desired.

Monitoring for xanthinuria

Sediment examination should be included in routine urinalysis at every scheduled recheck. Presence of xanthine crystalluria (NB: can be mistaken for urate crystals) should prompt review of the diet and water-intake management. Bladder ultrasound may be considered to assess for stone formation, particularly if the crystalluria is severe or there is evidence of urinary tract inflammation / haemorrhage.

Allopurinol dose adjustments

In dogs with persistent xanthine crystalluria despite appropriate dietary management. The risks and benefits of discontinuing or reducing (e.g. by 50% initially) the allopurinol need to be discussed. Subtherapeutic allopurinol dosing may promote development of drug resistance. Early allopurinol discontinuation may increase the risk of relapse.

Monitoring response to treatment

The majority of dogs improve clinically during the 1st month of treatment, usually within the first 1-2 weeks. Dogs with significant kidney disease have a poorer response but can still do well – both azotaemia and proteinuria can improve substantially in response to treatment. A reduction in parasitaemia (as determined using quantitative PCR) is usually seen quite quickly in dogs that were initially positive; the UPC and globulin levels may also improve quite quickly, but the response is more variable. Antibody titres remain increased for longer periods of time, even in the face of successful clinical treatment and usually only start to decline 3-6 months after starting treatment.

Scheduled monitoring is recommended at the following approximate time points after starting treatment: at 1 month, at 4 months, at ~8 months, and at ~12 months. Thereafter, every 6-12

months in those that are clinically well is sensible. Similarly, in clinically well dogs, scheduled monitoring every 3-4 months is recommended for the first year following discontinuation of treatment, increasing to every 6-12 months thereafter. Whether receiving treatment or not, where there is concern regarding relapse or treatment side effects dogs should be examined and diagnostic testing performed as appropriate.

Monitoring should include review of clinical signs and physical examination, as well as haematology, serum biochemistry, urinalysis, and blood qPCR (if previously positive). Repeat serology is not recommended until at least the 4-month recheck and only every 6-12 months thereafter. Use of a comprehensive *Leishmania*-focussed clinical scoring system can be considered (DOI: 10.1111/j.1365-3164.2009.00824.x.).

If there has been a response to treatment, clinicopathological changes will often normalise during the first 4 months of treatment. The 1-month testing is useful to evaluate the efficacy of the meglumine / miltefosine given. A marked improvement in test results suggests that the maintenance phase of treatment (i.e. allopurinol alone) can be entered. Rarely the improvement is not as good as expected and *consideration* can be made to giving meglumine (or miltefosine) for another 2-4 weeks – it is recommended to seek specialist advice before doing this.

When can I finish treatment?

After 6-12 months of successful treatment, consideration may be given to discontinuing allopurinol. Ideally, all clinicopathological parameters should be within reference range, the antibody titres borderline or negative, and (if previously positive) blood qPCR negative, before allopurinol treatment is stopped. If a bone marrow sample is available, a negative PCR provides further support for discontinuation. In some dogs, a mild proteinuria may be persistent and require specific management. For dogs with persistently high titres see below.

Relapses

Relapses are not uncommon or unexpected, even in dogs on continued allopurinol. For clinically well dogs, without concerning clinicopathological changes, there is no rationale to continue allopurinol beyond the first 6-12 months; indeed this is associated with increased risk of xanthine urolithiasis. For both induction agents, it is expected for 1 in 5 dogs to relapse within 2 years of treatment regardless as to whether they remain on allopurinol. Most of the dogs that relapsed in one study did not need a third treatment (DOI: 10.3390/pathogens12070864).

Immunologically, relapse is associated with a change in the immune response. Relapse is almost always associated with an increase in antibody titre and an acute phase protein response. Relapse usually manifests with the same signs as before, but not always.

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It is unclear why relapse occurs in most cases. In some dogs, particularly those that relapse rapidly after the induction phase has been completed, drug resistance is possible and has been described for all anti-*Leishmania* drugs (DOI: 10.1016/j.ijpddr.2018.08.002; DOI: 10.1016/j.ijpddr.2016.04.003; DOI: 10.1186/s13071-021-05100-x).

Persistent / increasing titres in the absence of clinical signs

Some "clinically well" dogs will have rising titres or persistently increased moderate to high titres. It is not clear whether these dogs are at risk of imminent progression to clinical disease. Dogs with subclinical infection can have persistent high titres in both endemic and (less commonly due to lack of repeated exposure) non-endemic countries. These are tricky cases and consensus as to how to manage them has not been achieved.

Findings of a careful clinical examination (paying particular attention to the skin, joints, and eyes) should be considered alongside a minimum of haematology, serum biochemistry, and urinalysis (including UPC) – to confirm the absence of subtle signs. Fine needle aspirates for cytology and *Leishmania* PCR may be considered for equivocal skin or ocular lesions, prominent lymph nodes, enlarged spleen, or bone marrow. Increased C-reactive protein may be suggestive of imminent onset of clinical disease.

"Clinically well" dogs with a prior history of clinical disease

In the absence of active disease, use of an induction agent is not recommended. Options are

i) If currently receiving allopurinol:
   a. Extend the course as there is concern that discontinuation would increase risk of relapse (especially if the titre is rising). *But* – there is no evidence to support the use of allopurinol beyond 12 months in preventing relapse and there is concern that continued use will promote resistance to allopurinol.
   b. Discontinue the allopurinol

ii) Assess response to immune-support medication (see above)

iii) A combination of the i) and ii)

Ideally, dogs should be regularly reviewed: if clinically well every 3-4 months for the first year after stopping anti-*Leishmania* treatment, then every 3-6 months where titres remain high, and at the time if clinical signs develop.

"Clinically well" dogs without a prior history of clinical disease

Anti-*Leishmania* treatment is not recommended. There is concern that unnecessary use could lead to resistance. The use of immune-support medication (see above) could be considered – particularly where C-reactive protein is increased and otherwise unexplained. Ideally, dogs should

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be regularly reviewed: if clinically well every 3-6 months where titres remain high / are increasing, and at the time if clinical signs develop.

Prognosis

Dogs with low infection loads (low serology, qPCR usually negative) can remain free of clinical signs for extended periods, potentially lifelong.

In dogs with mild disease prognosis is generally good, with moderate disease prognosis is considered good to guarded, while with severe disease prognosis is guarded to poor.

Treatment does not clear infection. Monitoring is important as described above. Dogs known to have been infected with *Leishmania* should never be used as blood donors or bred from, regardless of current stage. Immunosuppression should be avoided, if possible.

Prevention – vaccination and limiting exposure

Vaccination against leishmaniosis reduces the risk of clinical leishmaniosis in dogs that travel to endemic areas by around 70%. But it is not protective against infection and is not recommended in dogs with active or subclinical *Leishmania* infection. Vaccination induces antibodies that cross-react with conventional ELISA and IFAT *Leishmania* assays (but not all point-of-care assays). Vaccination will not induce PCR-positivity; PCR can still be used for diagnosis of *Leishmania* infection in a vaccinated dog. A helpful review regarding the effect of vaccination on testing can be found online (DOI: 10.1016/j.pt.2017.06.004)

The importance of vector (sand fly) control in the prevention of leishmaniosis cannot be overemphasised, even in vaccinated dogs. In dogs travelling to endemic areas, synthetic pyrethroids (repellent) should be used and they should be kept indoors when sand flies are active – in Europe this is from 7pm to 7am and from May to October.

In addition, there is evidence to support the use of domperidone prophylactically in dogs travelling (or intending to relocate to) a *Leishmania* endemic area. In a randomised clinical trial that recruited seronegative dogs living in an endemic area, use of domperidone reduced the development of both clinical disease and seroconversion in dogs (DOI: 10.1016/j.prevetmed.2014.03.010).

Risk to in contact dogs

In the absence of the sand fly vector, dog-to-dog horizontal transmission is possible (typically following prolonged close contact) and likely under diagnosed and reported.

Even though the known vector for *Leishmania* spp. (i.e. the sand fly) is not endemic in the UK, there have been cases of *autochthonous* dog-to-dog transmission in the UK from clinical cases to naive dogs with no travel history (DOI: 10.1002/vetr.1557; DOI: 10.1136/vr.105157; DOI: 10.1136/vr.l1268). These dogs had a history of prolonged / regular close contact with travelled

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dogs with clinical and subclinical *Leishmania* infection, either by sharing the same household or by spending extended periods of time in close contact (e.g. 'doggy day care').

Prophylactic control of ectoparasites (ideally including repellent activity) is recommended. NB: it is useful to know the heartworm status of these dogs prior to giving them anything that is microfilaricidal.

Risk to in contact humans

In the absence of the sand fly vector (in the UK) the risk of zoonotic transmission is currently considered to be **very low**.

In humans, *L. infantum* infection causes zoonotic visceral leishmaniasis, particularly in immunosuppressed adults and children. Direct transmission of *Leishmania* infection in the absence of sandfly vectors from dogs to humans has not been documented to date. However, in the presence of cutaneous lesions (particularly given that alternative differentials include zoonoses such as dermatophytosis) the wearing of gloves and routine hand hygiene would be considered prudent in the veterinary setting. Prophylactic control of ectoparasites (ideally including repellent activity) is also recommended.

The Human Animal Infections and Risk Surveillance group (HAIRS) has produced guidance regarding human health implications: https://www.gov.uk/government/publications/hairs-risk-assessment-canine-leishmaniosis

Leishmaniosis in cats

Feline leishmaniosis is rarely reported and has been reviewed elsewhere (DOI: 10.3390/pathogens12111351; DOI: 10.1016/j.crpvbd.2021.100035; DOI: 10.1186/s13071-022-05369-6). Clinical signs are very similar to those noted in dogs. Answers to most questions regarding feline leishmaniosis can be found within the LeishVet guidelines https://www.leishvet.org/fact-sheet-feline-leishmaniosis/. These were updated in March 2024.

The quantitative ELISA offered by **Langford Vets Diagnostic Laboratories (Acarus)** is optimised for the detection of canine antibodies and has not been validated for use in cats. The quantitative *Leishmania* PCR routinely offered by **Langford Vets Diagnostic Laboratories (Acarus)** is validated for the detection of *Leishmania* DNA in canine samples and the internal control assay detects canine DNA; however, it could be applied to the detection of *Leishmania* kDNA in feline samples, including modification to include a feline DNA internal control. Please contact the laboratory for advice if you have a cat with suspected leishmaniosis.

Leishmaniosis

Further advice

Our team are happy to provide advice on individual cases, including all vector borne disease – if you have specific questions, please submit these here Langford Vets - Advice service.

Last edited in May 2024 by Emi Barker, Jenny Reeve, & Claudia Gil Morales