# Article

## Causes, diagnostic signs, and the utility of investigations of fever in dogs: 50 cases

Cindy Chervier, Luc Chabanne, Mariam Godde, Maria I. Rodriguez-Piñeiro, Bertrand L. Deputte, Jean-Luc Cadoré

**Abstract —** This study aimed to determine the distribution of diseases causing fever in dogs in France. Dogs with fever were reviewed and 50 dogs were retrospectively assigned to disease groups. Fever profile and intensity, the time taken to reach a diagnosis, and inflammatory status were compared among groups. Almost half the dogs (48%) were diagnosed with non-infectious inflammatory diseases. No final diagnosis was reached in 14 dogs, 13 of which belonged to owners who did not wish to pursue the investigations. No association was found between disease group and the intensity of fever, fever profile, or serum C-reactive protein concentration. Cytological examinations were most frequently found to be the most important determinant for diagnosis (55.7%). This study confirms the predominance of non-infectious inflammatory diseases as causes of fever. Neither clinical nor biological factors were found to be predictive of disease group.

**Résumé — Etiologie, indices cliniques et biologiques, et utilité des examens complémentaires lors de fièvre chez le chien : étude de 50 cas.** Le but de cette étude est de déterminer les causes de fièvre chez le chien en France. Les chiens présentant une fièvre ont été revus et répartis rétrospectivement dans un groupe selon la cause de la fièvre; 50 chiens ont été inclus. Le profil de la fièvre et son intensité, le temps d'atteinte du diagnostic ainsi que le statut inflammatoire ont été comparés entre les groupes de causes de fièvre. Près de la moitié des chiens (48 %) présentaient une maladie inflammatoire non infectieuse. Aucune cause n'a pu être mise en évidence chez 14 chiens, mais pour 13 d'entre eux, les propriétaires n'ont pas souhaité poursuivre les investigations. Aucune association n'a été trouvée entre les groupes et l'intensité de la fièvre, le profil fébrile ou la concentration sérique de la protéine C-réactive. L'examen cytologique était la procédure la plus déterminante pour le diagnostic (55,7 %). Cette étude confirme la prépondérance des maladies inflammatoires non infectieuses comme cause de fièvre chez le chien. Aucun indice clinique ni biologique n'a été trouvé comme prédictif d'un groupe causal en particulier.

(Traduit par les auteurs)

Can Vet J 2012;53:525–530

## Introduction

Fever is a major challenge for diagnosis in both human and veterinary medicine. It may be caused by more than 200 diseases in humans and identification of its cause requires a logical, rational diagnostic plan. This plan should be based on knowledge of the various etiologies of fever in a given area and of clinical or biological indices (or both) predictive of disease type, together with evaluation of the utility of the diagnostic tests employed.

Internal Medicine Unit, Veterinary Campus of Lyon, VetAgro-Sup, 1 avenue Bourgelat, 69280 Marcy l'Etoile, France.

Address all correspondence to Dr. Jean-Luc Cadoré; e-mail: jl.cadore@vetagro-sup.fr

Use of this article is limited to a single copy for personal study. Anyone interested in obtaining reprints should contact the CVMA office (hbroughton@cvma-acmv.org) for additional copies or permission to use this material elsewhere.

In small-animal veterinary medicine, the etiological profile of fever has been reported in 2 retrospective studies involving 101 cases (1) and 66 cases (2), in which non-inflammatory diseases were the predominant cause of fever. In human medicine, the relative distribution of specific disease categories has changed with time. The frequency of fever due to non-infectious inflammatory diseases (NIID) and fever of unknown origin (FUO) has increased, whereas that of fever caused by infectious diseases and neoplasms has declined.

Some studies in humans have shown that certain clinical factors [such as the periodicity of fever (3,4)] and biological tests [sedimentation rate and hemoglobin level (5)] may be correlated with the likelihood of reaching a final diagnosis, and with particular disease groups in the case of a successful diagnosis. The identification of such diagnostic factors has not previously been attempted in veterinary medicine.

The aims of this study were to determine the distribution of diseases causing fever in dogs in France, and whether or not particular clinical (for example, fever profile) or biological (such as inflammatory status) factors are predictive of a particular

group of diseases, providing a clue to diagnosis. We also aimed to assess the utility of the investigations performed in the evaluation of febrile dogs.

## Materials and methods

We searched the medical database of the Veterinary Campus Hospital (VCH), Lyon, France for records of all dogs with fever examined between January 1, 2004 and December 31, 2009 (keywords for search: hyperthermia, FUO). The cases identified were retrospectively reviewed. Dogs with fever lasting more than 1 wk and with a peak temperature of at least 40.0°C on at least 1 occasion were included in the study.

We checked the records for the characteristics of the dogs (breed, age, and sex), time to referral (defined as the time between the first consultation with the referring veterinary surgeon and the first consultation at our hospital), fever profile, associated clinical signs ("clinical fever"), previous and current treatments, rectal temperature on admission, diagnostic procedures performed (those useful for diagnosis were noted), final diagnosis, time taken to reach a diagnosis, and duration of follow-up.

### Causes of fever: Final diagnosis

Dogs were retrospectively assigned to 1 of the following final diagnosis groups: infectious disease, non-infectious inflammatory disease (NIID) including immune-mediated diseases, neoplasm, and no final diagnosis. The dogs for which no final diagnosis was obtained comprised cases in which the owners did not wish to pursue the investigations and dogs with fever of unknown origin (FUO). Fever of unknown origin was defined as a fever lasting at least 1 wk and peaking at 40.0°C or more on at least 1 occasion, but for which no diagnosis was reached despite the use of a precise, multistage diagnostic plan, as proposed by Lunn in 2004 (6).

### Diagnostic signs

#### *Fever profile*

Febrile dogs were assigned to 1 of 2 categories: "intermittent fever," defined as several intermittent febrile episodes, or "continuous fever," corresponding to fever with remission during treatment and relapse after the end of treatment or fever that did not respond to treatment. Based on clinical presentation, isolated fever was defined as hyperthermia presenting with only the typical clinical signs of fever (lethargy) and without other clinical signs. Non-isolated fever was defined as hyperthermia with additional clinical signs. Hyperthermia was assessed on admission and dogs were classified as follows: fever absent (temperature $\leq$ 39.9°C), moderate (40.0°C $\leq$ temperature $<$ 40.5°C), severe (40.5°C $\leq$ temperature $<$ 41.0°C), or very severe (temperature $\geq$ 41.0°C).

#### *Inflammatory status*

Leukocytosis was graded as: absent [white blood cell (WBC) count $\leq$ 17 000/μL], mild (WBC $>$ 17 000 to $\leq$ 20 000/μL), moderate (WBC $>$ 20 000 to $\leq$ 25 000/μL), or severe (WBC $>$ 25 000/μL).

C-reactive protein (CRP) concentration was determined by an immunoturbidimetric assay (CRP Plus ref 981794, 340 nM) using an automated chemical analyzer (Konelab 30; ThemoScientific, Eragny Parc, Cergy Pontoise, France). This assay has been available since 2008.

### Diagnostic procedures and laboratory investigations

Routine hematological and biochemical analyses were performed by the Hematology and Biochemistry Laboratories of the VCH. Cytological examinations were carried out by a board-certified clinical pathologist. Cultures were submitted to the Bacteriology Laboratory at the VCH. Urinary sediments and cultures were examined after cystocentesis. For each dog, all the procedures performed were retrospectively classified as: determinant for diagnosis, helpful for diagnosis if positive, or helpful for diagnosis if negative.

### Time taken to reach a diagnosis

Dogs were assigned to 4 groups based on the time required to reach a diagnosis: early diagnosis (within 3 d of evaluation of the animal), intermediate diagnosis (between days 4 and 7), late diagnosis (between days 8 and 14), and very late diagnosis (after day 14).

### Statistical analysis

Nonparametric statistical analysis was carried out (7). Chi-squared tests were used to compare the distributions of cases with a theoretical uniform distribution. Mann-Whitney U-tests were used to compare means from 2 independent samples. A nonparametric one-way analysis of variance (ANOVA) (Kruskal-Wallis test, H statistic) was used to compare more than 2 samples. All tests were two-tailed, and differences were considered to be significant if $P < 0.05$.

## Results

### Animals

Fifty of 181 dogs that were presented with hyperthermia between January 1, 2004 and December 31, 2009 met the inclusion criteria. The remaining 131 dogs were excluded because they had peak temperatures less than 40.0°C ($n$ = 52) or because the fever lasted less than 1 wk ($n$ = 79). Twenty-seven breeds were represented and no one breed predominated.

The 50 dogs comprised 21 males (42%) and 39 females (58%). The median age of the dogs was 27 mo (range: 5 to 96 mo), with 25% of the dogs $<$ 13-months old and 75% $<$ 60-months old. The median ages of dogs with infectious, noninfectious inflammatory, or neoplastic disease or with no diagnosis reached were 18 mo (range: 8 to 84 mo), 36 mo (range: 5 to 96 mo), 84 mo (range: 72 to 96 mo), and 16 mo (range: 6 to 84 mo), respectively. The different types of disease occurred at significantly different ages, with neoplasms found in the oldest dogs ($P$ = 0.044).

### Causes of fever: Final diagnosis

Almost half the dogs (24 dogs) were diagnosed with NIID. Nine dogs had an infectious disease and 3 had neoplasm. In 28% of cases ($n$ = 14), no diagnosis was reached because the owners decided not to proceed with investigations in 13 cases and because the fever was classified as FUO in the final case.

**Table 1.** Utility of the investigations performed in the evaluation of febrile dogs

| Diagnostic procedures | Number of procedures that are the determinant for diagnosis | Number of procedures facilitating diagnosis when positive | Number of procedures facilitating diagnosis when negative | Number of procedures not helpful for diagnosis | Number of procedures performed |
|---|---|---|---|---|---|
| Hematology | 3 | 12 | 45 | 2 | 62 |
| Biochemistry | 7 | 13 | 111 | 1 | 132 |
| Imaging | 2 | 14 | 66 | 2 | 84 |
| Cytology/histology | 34 | 9 | 68 | 1 | 112 |
| Immunology | 9 | 2 | 56 | 1 | 68 |
| Bacteriology | 6 | 2 | 30 | 0 | 38 |
| Others | 0 | 0 | 2 | 1 | 3 |
| TOTAL | 61 | 52 | 378 | 8 | 499 |

## Diagnostic signs

### *Fever profile*

Fever was continuous in 28 of the 50 dogs. A continuous fever was noted in 4 of the 9 dogs with infectious disease, 14 of the 24 dogs with NIID, and 8 of the 14 dogs for which no diagnosis was reached. There was no association between fever profile and final diagnosis ($P > 0.05$).

An isolated fever was noted in 4 of the 9 dogs with infectious disease, 9 of the 24 dogs with NIID and 9 of the 14 dogs for which no diagnosis was reached. All dogs with neoplasms had additional clinical signs (nonisolated fever).

In the infectious diseases group, 3 of the 9 dogs had no fever on admission, 4 had moderate fever, and 2 had severe fever. In 75% of the dogs (18/24) with NIID, no hyperthermia was noted on admission. In 18 of the 32 dogs without hyperthermia on admission, the final diagnosis was NIID. One-third of the dogs with neoplasms had very severe hyperthermia on admission (> 41.0°C). Ten of the 14 dogs for which no diagnosis was reached did not have hyperthermia on admission, whereas moderate hyperthermia was noted in 3 dogs and severe hyperthermia in 1 dog.

The final diagnosis was not influenced by temperature on admission ($P = 0.137$) and there was no association between clinical fever and final diagnosis.

### *Time to referral*

Most dogs (80%) were admitted to the VCH following referral by the client's usual veterinarian. The mean (range) time to referral for all dogs was 3.8 (0.25 to 24) mo. The mean time to referral for dogs with intermittent fever (6.18 mo) was significantly greater than that for dogs with continuous fever (1.7 mo) ($P = 0.0009$).

### *Inflammatory status*

A WBC count was performed for all dogs and serum C-reactive protein (CRP) concentration was determined in 21 dogs. No leukocytosis was noted in 21 of the 50 dogs, whereas mild, moderate, and severe leukocytosis was noted in 5, 8, and 16 of the 50 dogs, respectively. Nine of the 16 dogs with severe leukocytosis were diagnosed with NIID.

Serum CRP concentrations were determined in 21 dogs and were within the normal range (< 10 mg/L) in 3 of the dogs (2 with inflammatory diseases and 1 with no diagnosis reached). Four of the 18 dogs with a serum CRP concentration above the upper limit of the normal range had very high CRP concentrations (> 40 mg/L) and 2 of these dogs had no fever on admission. Two of these dogs were diagnosed with NIID and no diagnosis was reached for the other 2. Serum CRP concentration did not seem to be influenced by the type of disease, if diagnosed, or by the absence of a final diagnosis ($P = 0.694$).

C-reactive protein concentration was compared between dogs with hyperthermia on admission ($n = 9$) and those without hyperthermia on admission ($n = 12$). All 3 dogs with CRP concentrations within the normal range had no fever on admission. All dogs with hyperthermia on admission had a CRP concentration above the upper limit of the normal range. Half of the dogs without fever on admission and with high CRP concentrations were already receiving treatment on admission. C-reactive protein concentration did not differ significantly between dogs with and without fever on admission ($P = 0.545$). The nature of the fever (continuous or intermittent) did not seem to have a significant effect on CRP concentration ($P = 0.279$).

We compared CRP concentrations between dogs with short ($n = 8$), moderate ($n = 3$), long ($n = 3$), and very long ($n = 1$) times to diagnosis. In all dogs with very high CRP concentrations (> 40 mg/L), a diagnosis was reached within 3 d. However, the time taken to reach a diagnosis, as categorized, did not differ significantly as a function of CRP concentration ($P = 0.827$).

## Diagnostic procedures

In total, 499 diagnostic procedures were carried out (mean: 10 procedures per dog). The utility of the investigations performed in the evaluation of febrile dogs is presented in Table 1. Biochemical investigations were the most frequent, accounting for 26.5% of all procedures performed, followed by cytology/histology (22.4%), imaging (16.8%), immunology (13.6%), hematology (12.5%), and bacteriology (7.6%). Cytology/histology procedures were most frequently the determinant for diagnosis (55.7%), whereas imaging was rarely determinant (3.3%). We found that 30% of the cytological or histological analyses performed were the determinant for diagnosis, versus only 2.4% of imaging examinations.

Among the procedures helpful for positive diagnosis, hematology, biochemistry, and imaging were the most useful, with

similar frequencies (23.1%, 25.0%, and 26.9%, respectively), whereas immunology and bacteriology were the least useful (in 3.8% of cases each). Overall, 19.4% of the hematological analyses performed were helpful for positive diagnosis.

The usefulness of the investigations was compared between dogs with an isolated fever (total number of procedures performed: $n$ = 209, or 9.5 per dog) and those with nonisolated fever ($n$ = 290, or 10.4 per dog). Cytology/histology analysis was most frequently the determinant for diagnosis, whether the fever was isolated (47.6%) or not (60.0%). Hematology (35.3%) was the examination most frequently helpful for diagnosis when positive in dogs with isolated fever, whereas biochemistry and imaging (31.4% for each other) were the examinations most frequently helpful for diagnosis when positive in dogs with nonisolated fever.

The usefulness of the investigations was also compared between disease groups. In dogs with infectious diseases, cytology, immunology, and bacteriology were similarly useful for diagnosis (35.3%, 23.5%, and 29.4%, respectively). By contrast, in dogs with NIID, only cytology was particularly helpful for diagnosis (accounting for 60% of all procedures leading to diagnosis, versus 2.5% for bacteriological examinations).

### Time taken to reach a diagnosis

A final diagnosis was reached for 36 of the 50 dogs (72% of all cases). The mean time to reach a diagnosis in these dogs was 10.8 d. The mean time to diagnosis was 6 d in dogs with infectious diseases, 13.5 d in dogs with NIIDs, and 3 d in dogs with neoplastic diseases. The mean time to diagnosis did not differ significantly among the disease groups ($P$ = 0.372). Mean time to diagnosis was longest in dogs with NIID, but this difference was not significant.

The mean time to diagnosis was longer in dogs presenting without fever on admission (14.68 d) than in dogs with fever on admission (4.64 d), although this difference was not statistically significant ($P$ = 0.158). The mean time to diagnosis was 12.75 d in dogs with treatment on admission and 9.2 d in dogs without treatment ($P$ = 0.606). Mean time to diagnosis did not differ significantly between dogs with and without fever on admission, whether they had treatment on admission (4.75 and 15.42 d, respectively; $P$ = 0.582) or did not have treatment on admission (4.6 and 13.8 days, respectively; $P$ = 0.22).

There was a trend towards later diagnosis in dogs with intermittent fever (15.94 d) rather than continuous fever (6.65 d; $P$ = 0.059). The mean time taken to reach a diagnosis was 17.5 d in dogs with isolated fever and 6.95 d in dogs with other symptoms ($P$ = 0.138).

### Treatment on admission

All the dogs had received treatment before admission to our hospital (antibiotics, anti-inflammatory drugs, others) and 26 dogs were taking medication at the time of admission. In 20 of these dogs, there was no fever on admission. Dogs with treatment on admission were significantly more likely to present with no fever on admission ($P < 0.05$). Significantly fewer dogs with treatment than dogs without treatment had fever on admission ($P$ = 0.011).

## Discussion

In this study, we evaluated the etiological distribution of fever in dogs in a particular region of France, more than one decade after the first such study, carried out in 1998 (1). Like previous studies (1,2), the present study confirms the preponderance of inflammatory diseases as causes of fever in dogs.

In this study, only dogs presenting with a fever lasting more than 1 wk and with a peak temperature of at least 40.0°C (rectal temperature) on at least one occasion were included. This duration was considered sufficient to rule out many self-limiting, transient or acute causes (such as acute viral infections). The cut-off value for fever used in our survey was similar to that used by Dunn and Dunn (1) in the largest retrospective study of fever in dogs, facilitating comparison. The inclusion criteria cited here define a "fever of origin yet to be determined." This term should be preferred to the common term "fever of unknown origin," which corresponds to a fever in which the cause remains elusive despite numerous investigations, and conditions for which the definition has changed over time or differs among authors.

In human medicine, FUO was first defined by Petersdorf and Beeson (8) in 1961 as i) an illness of at least 3 weeks' duration, ii) with fever (temperature > 38.3°C on several occasions), and iii) no established diagnosis after 1 wk of hospital investigation. Changes towards the greater use of outpatient management, numerous advances in diagnostic techniques, and more rapid diagnostic investigations led to the proposal of a new definition of FUO by Durack and Street (9) in 1991. They suggested a modification of the third criterion: fever with no diagnosis despite appropriate investigations after at least 3 outpatient visits or 3 days in hospital. This modification has never been validated, but a study (3) has shown that this updating of the definition does not affect the distribution of the different groups for cases with a final diagnosis, or the diagnostic approach. The quantitative criterion (a time-related criterion) has been replaced with a qualitative criterion [a list of numerous investigations to be performed before an unsolved prolonged fever may be labeled FUO (10,11)]. This has resulted in greater uniformity of the patients considered to have FUO, regardless of the individual experience of the investigators or the diagnostic facilities at the hospital and the duration of the diagnostic process.

There is no standard definition of FUO in veterinary medicine. There are no published guidelines or evidence-based recommendations for the diagnostic workup for fever in veterinary medicine, but we decided to use a qualitative criterion and followed a multistage diagnostic plan, as proposed by Lunn (6). The proportion of cases without a final diagnosis was high in our study (28%), as in previous studies, but only 1 case of true FUO was found. This can be accounted for by the large number of cases in which the owners decided not to pursue investigation and by the qualitative criteria used to define FUO; a prolonged fever was classified as FUO only after a long and precise list of procedures, regardless of the amount of time required for the exploration. Indeed, 11 and 19 dogs with FUO would have been identified if the definition of FUO had followed the third criterion of Petersdorf and Beeson (8) (fever defined as FUO if no diagnosis was reached within 7 d of investigations) or Durack

and Street (9) (within 3 d), respectively. This highlights the need for a clear and uniform definition of FUO, making it possible to compare results between studies.

Fever presents a major diagnostic challenge. It was not possible to assign a positive or negative predictive value for diagnosis to clinical or biological factors, but we focused on determining if the factors considered were predictive of a particular disease group. We found no significant difference between disease groups in terms of fever profile, clinical fever, fever intensity, or serum CRP concentration. However, the fever associated with cancer is often considered to be a low-grade fever in the absence of a paraneoplastic immune-mediated disease (12). The lack of association between serum CRP concentration and disease group is consistent with the findings of a previous study (13) for dogs with nonfebrile illnesses. However, in 1 study (1), mean fibrinogen levels were highest in dogs with miscellaneous diseases, followed by dogs with immune-mediated diseases and FUO. In another study (2), no significant difference in mean time to diagnosis was found between disease groups. We also found no correlation between time to diagnosis and disease group, but the mean time to diagnosis was longer in dogs with inflammatory diseases, consistent with the findings of a prospective study in 290 human patients (3). The mean time to diagnosis was also greater in dogs with intermittent or isolated fever than in dogs with continuous or nonisolated fever, although this difference was not significant. As in the study by Battersby et al (2), fever investigation was more time-consuming in dogs already on treatment and dogs without fever on admission than in dogs without treatment and dogs with fever on admission (although there was no significant difference between groups). Treatment should be stopped as soon as possible when referring dogs for evaluation, to shorten the time to diagnosis.

Cytology/histology examination was the most frequent determinant for diagnosis, as in previous retrospective studies (1,2) in which cytological findings were the determinant in 26% and 45% of cases in which cytology was performed, respectively. By contrast, imaging does not seem to be determinant, accounting for only 3.3% of the procedures determinant for diagnosis in this study. However, no magnetic resonance imaging (MRI) examinations were carried out. Such examinations would probably have increased the utility of imaging for fever diagnosis. Nevertheless, imaging was particularly helpful for diagnosis, accounting for 26.9% of all the procedures helpful for diagnosis when positive. The utility of this screening would probably be increased by the inclusion of scintigraphy (positron emission tomography in particular), but facilities for these techniques are not widespread in veterinary medicine. In human medicine (11), nuclear medicine plays an important role in the approach to fever diagnosis in clinical practice as the techniques used can determine both the location and the number of infectious, inflammatory, or neoplastic foci in all parts of the body, based on functional changes in tissues. These techniques do not directly suggest a final diagnosis, but they can be used to localize the areas in which a particular metabolic process occurs. Positron emission tomography with $^{18}$F-fluoro-deoxglucose (FDG) is the currently preferred method. A few reports (14,15) in veterinary medicine have focused on this new imaging technique and its potential for use in fever investigation in small animals.

The usefulness of investigations was compared between dogs with and without isolated fever. Surprisingly, the number of procedures performed was similar in the 2 groups. We expected more procedures to be carried out in dogs with isolated fever, due to the lack of clinical signs on which to base diagnosis. Hematology and biochemistry/imaging procedures were the procedures most frequently helpful for diagnosis in dogs with and without isolated fever, respectively.

No randomized controlled trial has focused on fever and the utility of diagnostic tests in veterinary medicine. The study herein provides useful guidance for the approach to diagnosis of the cause of fever in small animals. Given the retrospective nature of the study and the small number of cases, the level of evidence is lower than that in human medicine (16). Further studies are therefore required for the development of guidelines or evidence-based recommendations for the diagnostic investigation of fever. However, there is no diagnostic gold standard against which other diagnostic tests may be compared in cases of fever, and this may limit further studies. Moreover, the diagnostic yield of a test should not be demonstrated in an isolated manner, but within a precise, multistage approach, because the diagnostic utility of a test may differ at different stages of investigation.

In conclusion, as reported in recent studies, non-infectious inflammatory diseases seem to be the major cause of fever in small animals, followed by infectious diseases and neoplasms. A large percentage of cases remain undiagnosed. The precise definition of FUO resulted in the identification of only 1 case of FUO. Fever of unknown origin should be uniformly and clearly defined in small-animal veterinary medicine and we suggest the use of a qualitative rather than time-related criterion. Cytological investigation was the most determinant procedure for the diagnosis of fever; hematology, biochemistry, and imaging procedures were also useful. Prospective studies are required to provide evidence-based recommendations for approaches to the etiological diagnosis of fever in dogs. CVJ

## References


1. Dunn KJ, Dunn JK. Diagnostic investigations in 101 dogs with pyrexia of unknown origin. J Small Anim Pract 1998;39:574–580.
2. Battersby IA, Murphy KF, Tasker S, Papasouliotis K. Retrospective study of fever in dogs: Laboratory testing, diagnoses and influence of prior treatment. J Small Anim Pract 2006;47:370–376.
3. Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: The challenge continues. Arch Intern Med 2003;163:1033–1041.
4. Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin. Review of 45 cases and survey of the literature. Medicine (Baltimore) 1993;72:184–196.
5. de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:401–414.
6. Lunn KF. Fever of unknown origin: Appropriate choice for diagnostic tests. Proc. ACVIM Forum, Minneapolis, Minnesota, 2004, 22nd Year.
7. Siegel S, Castellan JJ, eds. Nonparametric Statistics for the Behavioral Sciences. 2nd ed. New York: McGraw-Hill, 1988:399.
8. Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. Medicine (Baltimore) 1961;40:1–30.
9. Durack DT, Street AC. Fever of unknown origin — reexamined and redefined. Curr Clin Top Infect Dis 1991;11:35–51.

10. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: The yield of a structured diagnostic protocol. Medicine (Baltimore) 2007;86:26–38.
11. Bleeker-Rovers CP, van der Meer JW, Oyen WJ. Fever of unknown origin. Semin Nucl Med 2009;39:81–87.
12. Cauvin A. Pyrexia of unknown origin in the dog. In practice 2008; 30:302–313.
13. Tecles F, Spiranelli E, Bonfanti U, Ceron JJ, Paltrinieri S. Preliminary studies of serum acute-phase protein concentrations in hematologic and neoplastic diseases of the dog. J Vet Intern Med 2005;19:865–870.
14. Peremans K, De Winter F, Janssens L, Dumont F, Van Bree H, Dierckx R. An infected hip prosthesis in a dog diagnosed with a 99mTc-ciprofloxacin (infecton) scan. Vet Radiol Ultrasound 2002;43:178–182.
15. LeBanc AK, Jakoby B, Townsend DW, Daniel GB. Thoracic and abdominal organ uptake of 2-deoxy-2-[18F]fluoro-D-glucose (18FDG) with positron emission tomography in the normal dog. Vet Radiol Ultrasound 2008;49:182–188.
16. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 2003;163: 545–551.