

Uncovering the Cause of Fever in Dogs



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The term *fever of unknown origin* (FUO) is often overused in veterinary medicine, as the number of patients in which a true cause of fever cannot be uncovered is relatively small.

In 1961, Petersdorf and Beeson first defined FUO in humans as *a fever $\geq 101^{\circ}\text{F}$ (38.3°C) that persists for greater than 3 weeks, with the diagnosis uncertain after one week of study in the hospital*. This definition has remained mostly intact today except for the requirement of in-hospital study.^{1,2} The duration of greater than 3 weeks was intended to eliminate cases of acute self-limited infectious disease (often viral) from the retrospective analysis of FUO cases.¹

When describing FUO in dogs, fever is usually defined as greater than 103.5°F to 104°F ($39.7\text{--}40^{\circ}\text{C}$), with no duration of fever specified.^{3,4} In animals, the path to revealing the cause of persistent fever can be lengthy and expensive but, in most patients, an etiology can be eventually identified (see **FUO in Animals: Often a Misnomer**).

CLINICAL CHALLENGES

When a patient presents with an elevated temperature, it is important to distinguish from

the outset whether the increase is due to fever or nonfebrile hyperthermia (see **Is It Fever or Hyperthermia?**).

Most dogs that present with fever have some abnormality on physical examination that helps guide the diagnostic process. Abnormal findings that present with fever may include, among others, lymphadenomegaly, joint effusion, spinal or paraspinal pain or discomfort, low-grade cough, abnormal findings on thoracic auscultation, enlarged and painful prostate or swollen testicles in intact dogs, resistance to manipulation of the neck and head, red and swollen gums, or abdominal discomfort on palpation.

A dog that presents only with vague client complaints of lethargy and hyporexia can be a particularly difficult diagnostic challenge when the only significant finding on routine physical examination is fever. Cryptic fever becomes even more challenging when:

- Routine diagnostic laboratory work fails to localize the disease process
- The only abnormal finding on routine diagnostics is inaccessible (eg, enlarged peribronchial lymph nodes)
- Evaluation of identified abnormalities (such as an aspirate of an enlarged lymph node) fails to suggest a definitive disease process (eg, reactive lymph node).

The veterinarian is then faced with the dilemma of determining which additional diagnostic tests to pursue, and pursuit of more advanced diagnostics can be curtailed by owner financial concerns that arise with high-cost/low-yield tests and owner compliance (or lack thereof).

DIFFERENTIAL DIAGNOSIS

Fever often results from an immune or inflammatory response, and most causes of fever can be classified as infectious, immune-mediated, or neoplastic (**Table**).^{2,5}

FUO in Animals: Often a Misnomer

Veterinary patients are often described incorrectly as having FUO when routine diagnostic testing—which can usually be completed over the course of a day—yields negative results. In these cases, the designation of FUO is often applied prematurely. The term should be reserved for patients in which *no etiology is revealed after an extensive workup*.

Another commonly used, yet erroneous, criterion for defining FUO is a fever that does not respond to empiric antibiotics. A response to antibiotics does *not* prove a bacterial cause for fever because a transient response may be associated with an anti-inflammatory effect of the antibiotic or the waxing and waning course of disease. Thus, the cause of fever remains unknown.

Is It Fever or Hyperthermia?

Fever implies an internal resetting of the hypothalamic set point, whereas the elevated body temperature in hyperthermia results from outside causes. Many veterinarians have embarked on misguided diagnostic or therapeutic pathways due to the presumption that an elevated rectal temperature is associated with inflammatory disease.

In my experience, it is not uncommon to see dogs with elevated rectal temperatures associated with anxiety, environmental conditions, exercise, drugs, and catheters/wraps. In fact, I have seen dogs that have presented with rectal temperatures

in the 103°F to 104°F range (even as high as 105°F) as a consequence of anxiety.

The presence of fever can be confirmed either by hospitalizing the dog for several hours or instructing the owner to take the dog's temperature at home when the pet is relaxed. Likewise, when a dog that is being treated in the hospital for a noninflammatory disease suddenly develops an elevated rectal temperature but no other signs (eg, cough), the first step should be removal of tight bandages and removal/replacement of intravenous catheters before investigation for a nosocomial infection or other source of fever.

Infectious Causes

With infectious causes of cryptic fever, many animals have evidence of some abnormality on physical examination or routine laboratory screening. However, even diskospondylitis, pyelonephritis, leptospirosis, and the deep mycoses may present with no specific abnormalities.^{4,6-10}

A recently detected cardiac murmur can indicate bacterial endocarditis, although the murmur may be missed early in the course of disease. However, it is just as likely the murmur has been present and undetected for some time and is not part of the current febrile disease.

Immune-Mediated Causes

Sterile inflammatory diseases are most commonly immune-mediated, and include immune-mediated polyarthritis (IMPA), steroid-responsive meningitis-arteritis (SRMA), and systemic lupus erythematosus. In some dogs, IMPA and SRMA can be more difficult to diagnose because:

1. Laboratory changes are often restricted to an inflammatory leukogram
2. Dogs with IMPA may have relatively subtle lameness and minimal joint effusion, presenting with more generalized stiffness and discomfort (which can also be confused as SRMA).¹¹

Lameness can sometimes be uncovered by hyperflexing a limb; then having the dog walk immediately afterward.

Some sterile inflammatory processes are not immune-mediated but can produce significant fever; these diseases include acute pancreatitis, pansteatitis, nodular panniculitis, granulomatosis, juvenile cellulitis, shar-pei fever, hypertrophic osteodystrophy, and panosteitis.^{3,4,12,13}

Neoplastic Causes

Fever may be seen with various cancers, most

commonly lymphoma, leukemia, multiple myeloma, hepatic neoplasia, and necrotic tumor masses. One would expect hematologic abnormalities on the complete blood count (CBC), but these changes can often be subtle and/or misleading. Unexplained hematologic abnormalities should be viewed as an invitation to perform a bone marrow examination—aspiration or biopsy—which often yields a diagnosis.

DIAGNOSTIC APPROACH

Initial Diagnostics

The initial diagnostic approach in a dog with unexplained fever should begin with signalment,

TABLE.

Causes of Persistent Fever in Dogs

Infectious	Bronchopneumonia Deep mycoses Diskospondylitis Leptospirosis Pyelonephritis Pyothorax Soft tissue abscess Tick-borne disease Toxoplasmosis or neosporosis
Immune-Mediated	Granulomatous meningoencephalitis Panniculitis Polyarthritis Steroid-responsive fever Steroid-responsive meningitis-arteritis Systemic lupus erythematosus
Neoplastic	Lymphoid leukemia Lymphoma Myeloma Other leukemias
Miscellaneous	Hypertrophic osteodystrophy Intervertebral disk disease ³ Pancreatitis, acute or chronic Panosteitis Portosystemic shunt ¹

patient history, physical examination, and laboratory diagnostics (see **Diagnosing Fever: A Stepwise Approach**, page 34). When the diagnosis is not readily apparent following the initial diagnostic approach, the clinician is faced with the option of a therapeutic trial or continued diagnostics.

Ask Yourself...

The question that needs to be asked and answered at every step of the way is: **Do I have reasonable information for a diagnosis and treatment plan?** This question should always be re-evaluated just before and after an antibiotic trial (either failure or success).

Therapeutic Trial

The goal of the therapeutic trial should be diagnosis (or, at least, elimination of a disease category); therefore, antibiotics should not be combined with antipyretics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Artificial resolution of fever due to antipyretic administration may improve the patient's demeanor but is rarely required and tends to delay and confuse the diagnosis.

Antibiotic selection is empiric and often based on prior experience or suspicions (eg, doxycycline in a dog with high tick exposure). Depending on the patient's condition, most antibiotic trials are administered for 48 to 72 hours before declaring failure and considering either an alternate antibiotic choice or the next step in diagnostics.

During this trial period, the patient can be stabilized with IV fluids and other supportive care, if required, or discharged to the client if relatively stable.

Further Diagnostics

Presuming there is no response to the therapeutic trial(s) and no distinctive localized findings to prompt more specific diagnostic tests, the next level of diagnostics should be pursued.

These tests, some of which may require referral to specialty practitioners, include:

- Cytology and blood cultures
- Serology or polymerase chain reaction (PCR)
- Antinuclear antibody testing
- Imaging, such as radiography and ultrasound
- Bone scan
- Bronchoscopy.

Cytology & Other Testing

Random cytologic sampling is often not valuable, but simple collections, such as peripheral lymph node aspirates, can be obtained easily. There are a variety of sites from which to sample, some more challenging than others, and diagnostics can include aspirates of apparently normal lymph nodes, joint taps, bone marrow aspirate, and cerebrospinal fluid (CSF) tap.

Serology or PCR may be indicated for certain

infectious diseases, and the specific selection of tests is often based on regional prevalence of such diseases.

Imaging

Abdominal radiographs and ultrasound (if available) are commonly pursued because it is difficult to palpate the abdomen in many dogs, especially those that are particularly deep chested. Abdominal radiographs are also important in the diagnosis of diskospondylitis. In the absence of identifiable abdominal pain or abnormalities on palpation, thoracic radiographs often have more value than abdominal radiographs.

Computed tomography or magnetic resonance imaging of the brain rarely has value in the absence of neurologic abnormalities; CSF analysis has surprisingly greater benefit and is less expensive.

DEFAULT DIAGNOSIS

When the clinician has exhausted the diagnostics or, at least, reached a reasonable confidence level that infectious disease is not present and there is no evidence of neoplasia, the default diagnosis is immune-mediated fever.

Corticosteroid trials must be administered appropriately; my protocol is to administer prednisone at 2 mg/kg Q 24 H (or 60 mg/M² for larger dogs) for a minimum of 3 weeks (presuming the patient's response is good), with gradual reduction by 25% every 3 to 4 weeks. If infectious disease is present, most dogs will deteriorate within 3 to 5 days of initiating a corticosteroid regimen.

LITERATURE REVIEW

Three large retrospective studies of fever in dogs offer a valuable perspective on the outcome of diagnostic investigations into fever.^{3,4,14} Although the studies were conducted in Europe, where prevalence and type of infectious diseases may differ from those seen in the United States, the general findings are relevant across canine populations.

Inclusion Criteria

Inclusion criteria for these studies were fairly straightforward. Two studies included dogs that had a recurrent or persistent fever (> 40°C [104°F] on at least one occasion) documented for 1 week or longer.^{3,14} In the other study, investigators searched patient records for the term *FUO* or *fever of unknown origin* in the letter from the referring veterinarian as well as documentation of a fever (> 39.7°C [103.5°F]).⁴

Diagnostic Results

The records of 217 dogs with fever were evaluated. The most common final diagnostic category was immune-mediated disease, which was present in 32% (69/217) of the dogs. This category included IMPA and SRMA, both of which commonly have localizing signs.

Diagnostic Approach

When additional diagnostic tests were performed, presumably based on an abnormal finding on physical examination or routine screening laboratory tests (CBC, serum biochemistry profile, urinalysis),

the diagnostic yield was fairly high. For instance, cytology (which was poorly defined in these studies but included aspirates of masses or enlarged lymph nodes, CSF or synovial fluid analysis, and evaluation of bronchoalveolar lavage samples) provided, or was crucial to, the diagnosis in 56% to 62% of the dogs, and bone marrow aspiration yielded a diagnosis in 64%.

However, diagnostics that are often performed as screening tests and not always chosen based on a specific identified abnormality had a much lower yield. Radiographs revealed a diagnosis in 48% of patients (22/46 dogs) in the study by Dunn and Dunn³ but in only 9.5% and 3.3% of the patients in

Over the past 6 to 8 years, clinicians at Kansas State University Veterinary Health Center have identified more than 50 dogs with fever and a variety of clinical signs, including facial cellulitis, lymphadenomegaly, polyarthritis, hematologic abnormalities, hepatic enzyme elevation, and general malaise.

Diagnostic Findings

The most common cytologic finding from aspirates of the affected organ or tissue in these patients was pyogranulomatous (sometimes just suppurative) inflammation with no visible organism.

These findings led to a consideration of several diagnoses—fungal disease, systemic lupus erythematosus, or IMPA. However, the antinuclear antibody tests were negative and the polyarthropathy did not respond as expected to corticosteroids (although, often with very little detrimental effect other than the disease did not resolve completely).

The pursuit of this disease as infectious began when a holiday delayed an exploratory surgery on a febrile dog with pyogranulomatous hepatitis (from a liver aspirate). The dog was serendipitously administered enrofloxacin and azithromycin and responded completely to this combination, with no surgery needed.

Use of Two Antibiotics

Subsequently, it was discovered that other dogs with pyogranulomatous inflammation of no apparent cause responded completely to a combination of:

- ▶ A fluoroquinolone (enrofloxacin, 7.5–10 mg/kg PO Q 24 H or 5 mg/kg PO Q 12 H) **or**
- ▶ Ciprofloxacin, 15–20 mg/kg PO Q 24 H **and**
- ▶ Azithromycin, 5 mg/kg Q 24 H.

When dogs respond (eg, resolution or reduction of fever, cellulitis) to this antibiotic combina-

tion, they show dramatic improvement within 48 hours and the typical protocol is to proceed with a 6-week course; then carefully monitor the dog over the following 6 months for relapse. As with all antibiotic trials, if dogs do not respond within 72 hours, the trial should not be continued.

Ongoing Investigation

This treatment approach is based on the assumption that patients likely have bartonellosis or are infected with an unidentified unculturable organism even though:

- ▶ Bartonellosis has not been confirmed with PCR or serology testing in these dogs
- ▶ Use of this antibiotic combination varies from other treatment recommendations for bartonellosis.

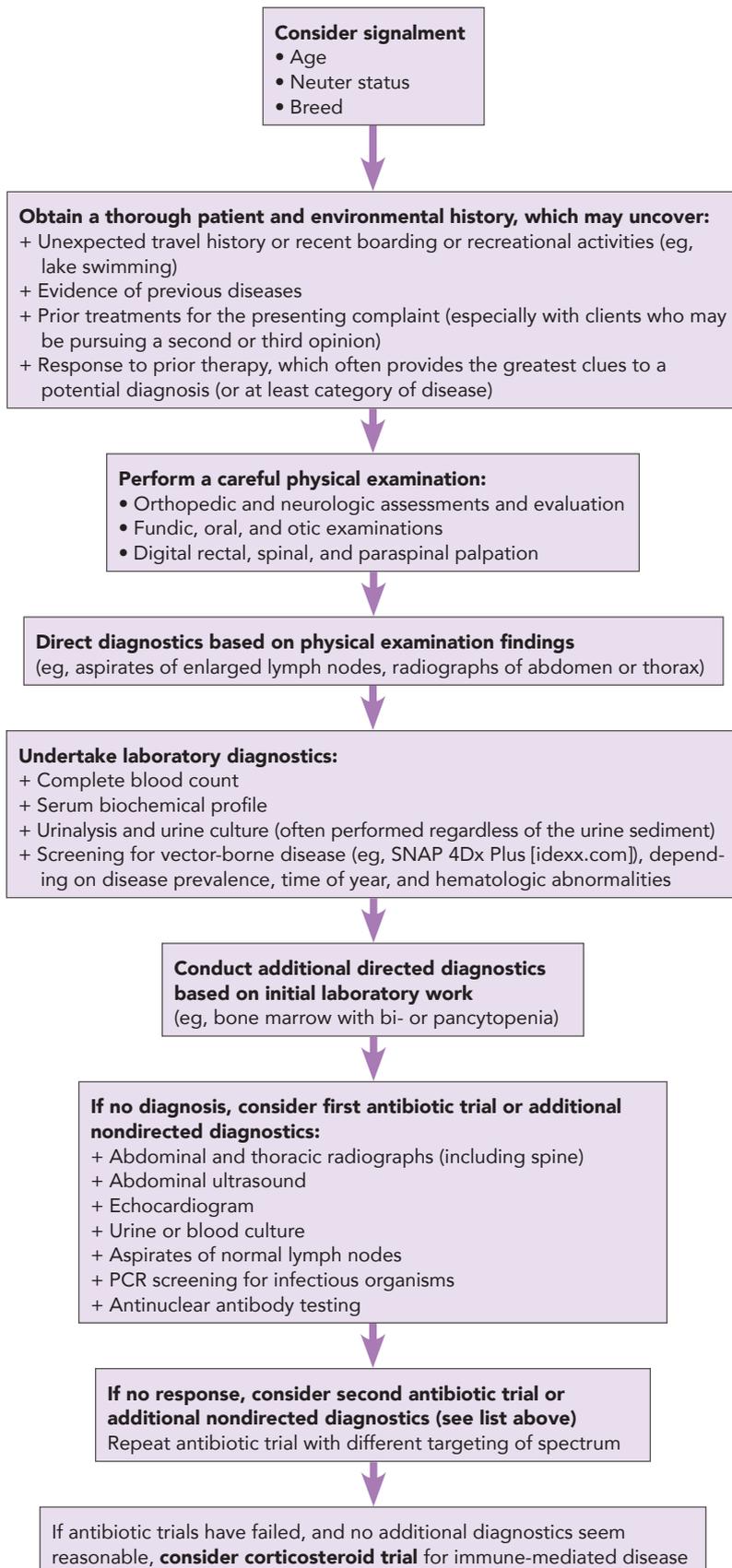
Bartonellosis has been reported in dogs with fever and pyogranulomatous inflammation in various organs,¹⁵⁻¹⁸ and the investigation into the dogs at Kansas State University continues.

Note on Ciprofloxacin

Some veterinary professionals feel that ciprofloxacin has unpredictable absorption and pharmacokinetics and, therefore, should not be used in dogs due to the results of a 2012 study.¹⁹ That study was conducted on 6 beagles that were fasted for 18 hours; 4 demonstrated high levels of absorption when administered ciprofloxacin, while 2 had poor absorption. A study comparing oral ciprofloxacin and norfloxacin in 4 beagles also noted inconsistent absorption of ciprofloxacin.²⁰ In contrast, a 1990 study on 4 mixed breed dogs (range, 16.4–27.3 kg) did not demonstrate large variations in pharmacokinetic variables.²¹ Therefore, a study involving a larger number of dogs receiving ciprofloxacin in real-world conditions (ie, with food) is needed to understand the prevalence of variable absorption among dogs.

Unpublished Observations from Kansas State University: Dual Therapy for Antibiotic Trials

DIAGNOSING FEVER: A STEPWISE APPROACH



the studies by Battersby et al⁴ and Chervier et al,¹⁴ respectively.

Although thoracic and abdominal radiographs were reportedly obtained in almost all dogs in the studies by Dunn and Dunn and Battersby et al, diagnoses were most commonly acquired from lesions identified on bony structures (eg, osteomyelitis, diskospondylitis, hypertrophic osteodystrophy).^{3,4} Chervier et al did not specify what type of radiographs were obtained.¹⁴

Likewise, abdominal ultrasonography, PCR testing for vector-borne disease, and serology for toxoplasmosis and neosporosis infrequently yielded a diagnosis.⁴ These methods failed to yield a diagnosis in 19/101³, 15/66⁴, and 14/50¹⁴ dogs.

Effect of Therapy

In the study by Battersby et al, therapy administered in the 24 hours before referral increased the time necessary to obtain a diagnosis.⁴ Chervier et al also looked at the effect of prior treatment, and although the mean time to diagnosis was longer in the group that had received prior treatment (12.75 versus 9.2 days in those that had not received prior treatment), this finding was not statistically significant.¹⁴

The findings by Battersby et al emphasize the need to resist the knee-jerk response to administer anti-inflammatories (NSAIDs or glucocorticoids) in response to fever⁴—a reaction often referred to as *fever phobia* in human medicine.²² Although fever may be a marker for a serious and life-threatening disease process, no evidence demonstrates that fever itself will result in organ damage or other serious consequences.²³

Although an antibiotic trial is often recommended and frequently employed in the workup of fever, antibiotics should be administered only after target areas have been sampled (eg, blood, urine, or abdominal fluid for culture or PCR). It is important that no additional antimicrobials or anti-inflammatories that may confuse the interpretation of the response be administered concurrently.

Outcomes

Outcomes for dogs with FUI were discussed in only one of these studies, with nearly half the dogs (7/15) demonstrating resolution of fever without treatment, 3 responding to antibiotics, and 2 requiring glucocorticoids.⁴ Chervier et al highlighted the importance of client compliance in obtaining a diagnosis: of 14 dogs in which a diagnosis was not obtained, failure of clients to pursue diagnostic

investigation was the reason for lack of diagnosis in 13 patients.¹⁴

IN SUMMARY

Uncovering the cause of fever in dogs is usually a straightforward process. For those in which the etiology is not easily uncovered, however, an ordered and logical diagnostic and treatment protocol helps categorize the etiology (ie, infectious, immune-mediated, neoplastic)—even if the ultimate diagnosis is vague (eg, immune-mediated fever).

CBC = complete blood count; CSF = cerebrospinal fluid; FUO = fever of unknown origin; IMPA = immune-mediated polyarthritis; NSAID = nonsteroidal anti-inflammatory drug; PCR = polymerase chain reaction; SRMA = steroid-responsive meningitis-arteritis

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