

The Diagnostic Approach to Fever of Unknown Origin in Dogs*

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Abstract: Identifying the cause of a fever of unknown origin (FUO) in dogs presents a considerable diagnostic challenge. The diagnostic workup can be frustrating for veterinarians and clients, especially when it fails to reach a final diagnosis after extensive testing. Fortunately, most causes of FUO can be found or treated successfully. This article discusses FUO in dogs and provides information about common causes, the diagnostic approach, and potential treatments.

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T rue fever (pyrexia) is defined as an increase in body temperature due to an elevation of the thermal set point in the anterior hypothalamus secondary to the release of pyrogens.¹ With hyperthermic conditions other than true fever, the hypothalamic set point is not adjusted.¹ Nonfebrile hyperthermia occurs when heat gain exceeds heat loss, such as with inadequate heat dissipation, exercise, and pathologic or pharmacologic causes.¹

Dogs with true fever typically have body temperatures between 103°F and 106°F (39.5°C to 41.1°C).² Prolonged body temperatures above 106°F are dangerous and can result in organ failure, disseminated intravascular coagulation, systemic inflammatory response syndrome, and death.^{1,3} Such temperatures are usually seen with nonfebrile causes of hyperthermia rather than with true fever.⁴ Temperatures less than 106°F are unlikely to be harmful and may be beneficial because they constitute a protective response to inflammation.^{1,5}

The term *fever of unknown origin (FUO)* is used liberally in veterinary medicine.⁵ It should be used to identify a fever that does not resolve spontaneously, that does not respond to antibiotic treatment, and for which the diagnosis remains uncertain after an initial diagnostic workup.⁵ Along with a thorough history and physical examination, initial diagnostics should include a complete blood count (CBC),

serum biochemistry profile, and urinalysis with antimicrobial culture. The cause of fever in most dogs is an infection that either is found during the initial workup or responds to antibiotic treatment; therefore, most dogs do not have a true FUO.⁵

Differential Diagnosis

The differential diagnosis for FUO in dogs is extensive, and development of an algorithm covering all causes is not feasible. Some causes of FUO in dogs are listed in **BOX 1**.^{2,4,5} Most FUOs are caused by a common disease presenting in an obscure fashion.⁶

Current information in the veterinary literature regarding FUO in dogs is limited.^{1,5} Infectious, immune-mediated, and neoplastic diseases are all important and common causes.^{2,5,7,8} About 10% to 15% of FUOs in dogs remain undiagnosed despite thorough diagnostic evaluation.⁵ The prognosis for undiagnosed FUO in dogs is not known. However, a retrospective study⁷ revealed that in 13 of 14 dogs with undiagnosed FUO, the fever either resolved spontaneously or responded to antibiotics, NSAIDs, or corticosteroids.

Clinical Approach

The diagnostic approach must be tailored to the patient. It should be guided by history and physical examination findings, simple laboratory testing, and the potential causes common to the geographic location.^{9,10} A three-stage approach, such as the one presented in **BOX 2**, is commonly

WEB
EXCLUSIVE



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*A companion article about fever of unknown origin in cats begins on page 26.

used.^{2,4,5} Communication with the owner is of utmost importance to ensure understanding of the time and financial commitment that may be required to obtain a definitive diagnosis. Fortunately, a diagnosis can be obtained in most circumstances, and many causes are treatable or manageable.⁸

All medications should be discontinued to help rule out a drug-induced fever. If the fever persists beyond 72 hours after medication cessation, a drug reaction can be ruled out.¹¹

History and Physical Examination

Obtaining a thorough history is the first step of a successful diagnostic approach. Clients should be questioned carefully about specific

or subtle clinical signs (historical, intermittent, and current) because these may help localize the fever source. A history of stiffness may suggest joint disease, but fevers can present similarly.³ Often, diagnostic clues are not readily apparent on physical examination, so repeated detailed physical examinations are essential (by multiple clinicians, if possible).¹⁰ Careful attention should be paid to the whole body—pulses, skin, mucous membranes, oral cavity, lymph nodes, heart, abdomen, bones and joints, and rectum. Repeated fundic and neurologic examinations are also important to identify subtle changes. As the disease progresses, new clues may emerge to help guide the next diagnostic steps.

BOX 1

Potential Causes of Fever of Unknown Origin in Dogs^{2,5}

- ▶ **Bacterial infection (focal or systemic):** Bacteremia, infective endocarditis, septic arthritis, osteomyelitis, diskospondylitis, septic meningitis, pyothorax, pyelonephritis, prostatitis, stump pyometra, peritonitis, deep pyoderma, abscess
- ▶ **Bacterial diseases:** Brucellosis, bartonellosis, borreliosis, leptospirosis, mycoplasmosis (hemotropic and nonhemotropic), tuberculosis and other mycobacterial diseases, diseases caused by L-form bacteria (e.g., cellulitis, synovitis)
- ▶ **Viral:** Canine distemper, parvovirus
- ▶ **Rickettsial:** Ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, salmon poisoning
- ▶ **Fungal:** Histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis
- ▶ **Protozoal:** Toxoplasmosis, neosporosis, babesiosis, trypanosomiasis, hepatozoonosis, leishmaniasis
- ▶ **Immune-mediated diseases:** Immune-mediated hemolytic anemia, polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, meningitis, steroid-responsive neutropenia and fever
- ▶ **Neoplastic:** Lymphoma, leukemia, multiple myeloma, malignant histiocytosis, necrotic solid tumors
- ▶ **Noninfectious inflammatory diseases:** Lymphadenitis, panniculitis, pancreatitis, pancreatitis, pancreatitis, granulomatosis
- ▶ **Miscellaneous:** Portosystemic shunt, drug reaction, toxin, shar-pei fever, metabolic bone disorders, idiopathic causes

Complete Blood Count and Serum Biochemistry Profile

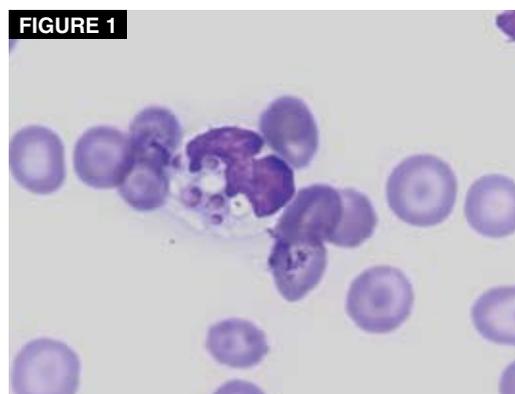
CBC and serum biochemistry profile abnormalities in dogs with FUO are generally non-specific, but they may indicate a need for further diagnostic tests. Every CBC should be accompanied by a blood smear evaluation to detect morphologic changes and parasites. Frequently, multiple blood smears and careful scanning are necessary to find infectious organisms (**FIGURE 1**). Sometimes only one organism will be seen on an entire slide. It is wise to save serum for serologic testing or other special tests that may be crucial in the future. A serum bile acids assay may be indicated because fever may be the only predominant clinical sign in dogs with portosystemic shunts.¹²

Urinalysis with Culture

A urine sample obtained via cystocentesis (unless contraindicated) should be submitted

QuickNotes

Urine culture should be conducted for all dogs with fever of unknown origin.



HISTOPLASMA ORGANISMS found on a blood smear from a dog.

Courtesy of Dr. Ty McSherry

BOX 2

Staged Diagnostic Approach to Fever of Unknown Origin in Dogs^{2,4}**Stage 1**

- ▶ Take a thorough history.
- ▶ Stop all medications to rule out drug-induced fever.
- ▶ Perform a meticulous physical examination, including fundic and neurologic examinations.
- ▶ Obtain samples for CBC, blood smear, and serum chemistry profile.
- ▶ Save serum for serology or other testing.
- ▶ Obtain a urine sample for complete urinalysis and urine culture.
- ▶ Submit a sample for urine protein:creatinine ratio if proteinuria and inactive sediment are present.
- ▶ Conduct fecal centrifugation and fecal cytology, if indicated.
- ▶ Consider obtaining thoracic and abdominal radiographs.
- ▶ Consider trial antibiotics if bacterial infection is suspected (e.g., doxycycline if ehrlichiosis is suspected).
- ▶ If necessary, proceed to stage 2.

Stage 2

- ▶ Repeat stage 1 tests as indicated.
- ▶ Obtain thoracic and abdominal radiographs if not obtained in stage 1.
- ▶ Conduct abdominal and other ultrasonography as indicated.
- ▶ Conduct echocardiography if a heart murmur is present.
- ▶ Conduct heartworm testing, if indicated.
- ▶ Conduct fine-needle aspiration with cytology of masses, lymph nodes, and fluids (cyst, pleural, peritoneal, prostatic wash), if indicated.
- ▶ Conduct blood culture.
- ▶ Conduct arthrocentesis.
- ▶ Conduct fecal cultures, if indicated.
- ▶ Conduct bone marrow aspiration if warranted by CBC results.
- ▶ Conduct serology for infectious diseases.
- ▶ Obtain long bone and joint radiographs.
- ▶ Conduct protein electrophoresis, if indicated.
- ▶ Conduct an immune panel, if indicated.
- ▶ If necessary, proceed to stage 3.

Stage 3

- ▶ Repeat stage 1 and 2 tests as indicated.
- ▶ Conduct echocardiography even if no murmur is present.
- ▶ Conduct transesophageal echocardiography.
- ▶ Conduct bone marrow aspiration even if CBC results are normal.
- ▶ Perform biopsy as indicated.
- ▶ Conduct bronchoscopy and bronchoalveolar lavage as indicated.
- ▶ Conduct cerebrospinal fluid analysis.
- ▶ Conduct dental radiography.
- ▶ Consider computed tomography, magnetic resonance imaging, nuclear imaging, or positron emission tomography.
- ▶ Conduct laparoscopy or thoracoscopy as indicated.
- ▶ Consider exploratory celiotomy.
- ▶ Administer trial antibiotic or antifungal therapy.

CBC = complete blood count

for a complete urinalysis with bacterial culture even if sediment is inactive. These tests should be repeated, especially if there is a history of lower urinary tract disease, as a negative urine culture does not rule out infection. Further diagnostic testing could include urine protein:creatinine ratio if proteinuria is present with inactive sediment.

Radiography

Two-view abdominal and three-view thoracic radiographs should be obtained if the minimum database does not reveal the cause of the fever. Total body radiographs can help aid in the diagnosis of masses, pneumonia, pyothorax, or other infections. Joint radiographs can aid in the diagnosis of an erosive immune-mediated polyarthritis.³ Other anatomic areas to radiograph include long bones (especially in young dogs), the spine, and dental structures (tooth root abscesses, masses). Special contrast radiographic studies can focus on other body systems (urogenital, spinal, gastrointestinal).

Ultrasonography

Abdominal ultrasonography allows for evaluation of organ parenchyma and can detect lesions not apparent on survey radiographs. It can also assist with fine-needle aspiration or biopsy if needed. Thoracic ultrasonography can be conducted if abnormalities (e.g., pleural effusion, cysts, masses) are detected on radiographs. When thoracic disease is not radiographically evident, ultrasonography is not rewarding because the lungs obscure intrathoracic anatomy.¹³ Ultrasonography can also be used to evaluate ocular (including retrobulbar), ventral cervical (thyroid/parathyroid, lymph node, salivary gland), and musculoskeletal (skin, subcutaneous, joint, muscle) regions if indicated.¹⁴⁻¹⁶

Echocardiography

Echocardiography should be conducted in dogs with FUO and a heart murmur, especially a new or diastolic murmur. Vegetative lesions must be differentiated from proliferative myxomatous valve degeneration. Dogs with infective endocarditis are usually medium to large breeds that do not tend to have myxomatous valve degeneration.¹⁷ Echocardiography can also be used to evaluate for a heart base mass if one is clinically suspected.

Blood Culture

Blood cultures should be conducted (preferably during a pyrexemic episode) for all dogs with FUO, especially those with a heart murmur, bounding pulses, lameness (polyarthritits), back pain (diskospondylitis), or urinary tract infection, as the latter three conditions can be sequelae to endocarditis.¹⁷ It is common for dogs with positive blood cultures to have isolation of the same organism from other tissue or fluid sites (cardiac, urinary, spinal).¹⁸ Aseptic techniques for obtaining samples are described elsewhere.^{2,19,20} The volume of the blood sample is more important than the timing; larger volumes are associated with an increased diagnostic yield in human medicine.^{19,21,22} Patient size determines the amount of blood to be drawn. As a general guideline, 16 to 20 mL of blood should be obtained from large dogs, and 5 mL of blood should be obtained from cats and small dogs.² The blood should be divided evenly and placed aseptically into aerobic and anaerobic blood culture vials (~70-mL vials for large patients, and ~20-mL vials for small patients).² If the patient's size allows, a second blood sample can be obtained immediately from a different site and divided as described above.² If the dog has recently received antibiotics, blood culture vials with resins that bind antibiotics should be used.^{2,19} Evidence suggests that recovery is improved in samples from blood culture resin vials because the resins may absorb inhibitors other than antibiotics²³; therefore, use of these vials for all blood samples may be warranted. *Bartonella* spp are emerging as an important cause of culture-negative infective endocarditis in dogs; therefore, submission of samples for *Bartonella* polymerase chain reaction (PCR) testing as well as serology is recommended in suspected cases.²⁴ Blood culture PCR techniques are being used in human medicine and may be valuable for use in dogs for detecting other infections in the future.²⁵

Cytologic Examination

Fine-needle aspiration with cytology should be conducted on any suspicious masses or lymph nodes, fluid accumulations, or abnormal organs. Cytology can be rewarding in the diagnosis of many infections as well as in the identification of abnormal cells (**FIGURES 2 AND 3**). Impression cytology (nasal

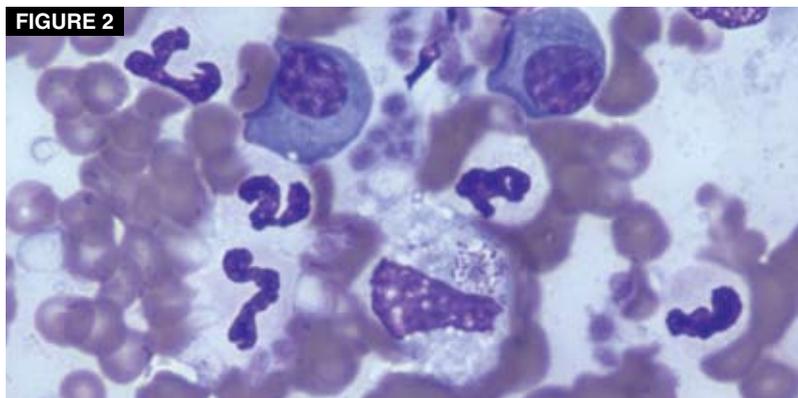


FIGURE 2
MORULAE in macrophages in a splenic aspirate from a dog infected with *Ehrlichia canis*.

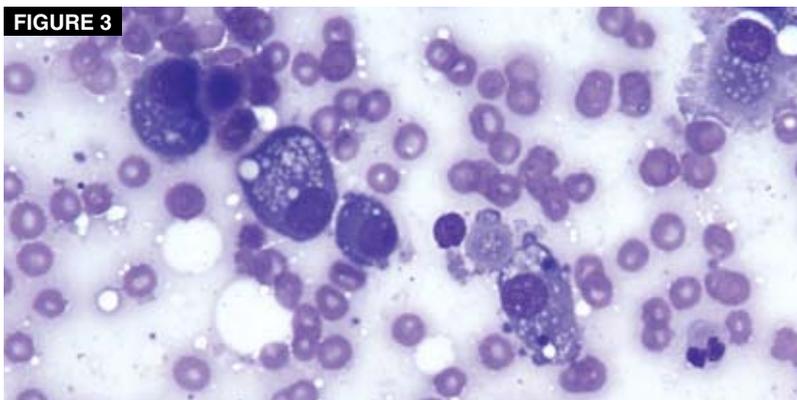


FIGURE 3
FINE-NEEDLE ASPIRATE from a spleen in a dog with malignant histiocytosis.

planum, skin, feces) can also be conducted if indicated. Fluid samples should be submitted for bacterial culture if the sample quantity is sufficient.

Bone Marrow Evaluation

Bone marrow aspiration should be conducted early in the evaluation of dogs with FUO if CBC abnormalities consistent with bone marrow disease are present. It should be considered in later diagnostic stages if no definitive diagnosis has been made, even if the CBC is normal, because neoplasia and infectious diseases can be common causes of FUO in dogs.^{2,8}

Arthrocentesis

Immune-mediated polyarthritits is a common cause of FUO in dogs even when no signs of arthritis are present (**FIGURE 4**).^{7,8} Arthrocentesis should be conducted on several joints and the samples submitted for cytologic evaluation (EDTA microcontainer) and possibly bacterial culture (aerobic, anaerobic, and mycoplasma). Infectious arthropathy needs to be ruled out

QuickNotes

Arthrocentesis can yield critical diagnostic information for many dogs with fever of unknown origin.

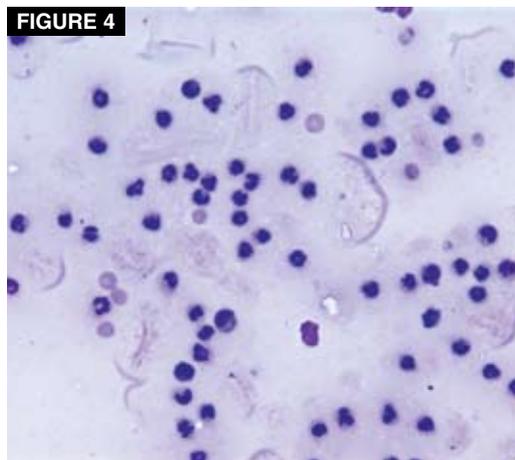


FIGURE 4
JOINT FLUID from the tarsus of a dog with immune-mediated polyarthritis.

Courtesy of Dr. Iy McSherry

if suppurative inflammation is seen on cytology because samples from septic joints do not always contain degenerate neutrophils, and a negative joint culture does not rule out infection.²⁶ If only a small sample can be obtained, it should be used for direct cytology. Otherwise, it is recommended to submit synovial fluid samples in blood culture medium to improve the diagnostic yield.²⁶ Synovial membrane biopsy with culture can also be considered.²⁶ Bacterial endocarditis can cause true infective arthritis or immune-mediated arthritis, and the two conditions must be differentiated.²⁷ Immune-mediated polyarthritis tends to involve the carpi and tarsi, whereas infective arthritis frequently involves larger joints (e.g., stifle, elbow, shoulder).²⁷ If immune-mediated polyarthritis is suspected, serology for rickettsial disease and a heartworm test may be indicated.²⁷

Serology

Serum samples should be submitted for fungal and rickettsial disease testing if these diseases are clinically suspected and if patient history indicates possible exposure. These tests should not be used as screening procedures in the hope that something abnormal will be found. Because *Toxoplasma* and *Neospora* spp are ubiquitous protozoal parasites, paired serum antibody titers for IgG and IgM should be submitted if a diagnosis continues to be elusive. A single high IgM indicates active or recent infection, and a fourfold IgG rising titer confirms infection.²⁸ It is important to remember that a negative antibody titer does not rule out infection and that a single positive titer implies either

exposure (e.g., fungal disease, most rickettsial diseases) or previous infection (e.g., protozoal disease) and does not necessarily correlate with active disease or current clinical signs.²⁸

Immunodiagnostic Screening Panels

Immunodiagnostic panels (antinuclear antibody, rheumatoid factor, Coombs) are typically unrewarding in dogs with FUO for several reasons, including the potential for false-positive results.^{2,7,8} Antiplatelet antibody tests and serum protein electrophoresis can be conducted if thrombocytopenia or hyperglobulinemia, respectively, is present.

Other Diagnostic Tests

Other diagnostic tests, such as prostatic wash, cerebrospinal fluid analysis, and bronchoscopy with bronchoalveolar lavage, should be considered if clinical abnormalities suggest prostatic, neurologic, or respiratory disorders, respectively. Samples should be submitted for cytologic evaluation as well as aerobic and anaerobic bacterial culture if quantity permits. Bronchoalveolar lavage samples should also be submitted for mycoplasma and slow-growing fungal cultures.

Advanced Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) should be used to help delineate diagnosed conditions or when the diagnosis remains equivocal.¹⁰ Nuclear scintigraphy is being used more frequently in veterinary medicine to detect infections and may be a valuable tool in the investigation of FUO in dogs.²⁹ Another promising imaging modality being used in human medicine, called *image fusion*, is the combination of positron emission tomography (PET; a type of nuclear imaging) and CT. A few reports of the use of image fusion in dogs demonstrate that this technique could play an important role in investigating canine FUO.³⁰⁻³³

Biopsy

If fine-needle aspiration cytology cannot provide a definitive diagnosis, a biopsy may be helpful. In one study,⁷ biopsy samples submitted for histopathology enabled a diagnosis in 15 of 17 dogs with FUO. Tissue samples can be obtained percutaneously (with or without imaging assistance); via endoscopy, laparos-

TO LEARN MORE

For more information on special tests that can be used in diagnosing the cause of FUO in dogs, please visit the **Web Exclusives** section of CompendiumVet.com.

copy, or thoracoscopy; or surgically during laparotomy. Submission of tissue samples for histopathology and possibly bacterial or fungal cultures is recommended. Exploratory celiotomy with biopsy is indicated only by the results of diagnostic testing.⁸ The diagnostic yield of exploratory celiotomy in a dog with no indication for surgery is unknown.

Treatment

Specific treatment is based on the definitive diagnosis, if found. Administering intravenous fluids or placing a fan blowing toward the cage can be used to reduce the temperature in hospitalized patients. In dogs for which extensive investigation yields no diagnosis, judicious use of antibiotic therapy may be warranted. The choice of antibiotic depends on the suspected bacterial agent. If no response is seen after 72 hours with appropriate dosing, another antibiotic that covers a different spectrum may be chosen.³⁴ If a bacterial infection is suspected in a severely ill patient, the four-quadrant approach—choosing an antibiotic or combination of antibiotics that is effective against aerobic, anaerobic, gram-positive, and gram-negative organisms—is recommended.³⁴ If antibiotic therapy is not successful, NSAIDs can be administered, keeping in mind the potential side effects.^{5,7} Fever can result in considerable malaise, dehydration, and anorexia; therefore, clinicians must decide in each case whether NSAIDs could be beneficial.⁴ Antipyretics (e.g., ketoprofen, flunixin meglumine, dipyrone) should be used with caution because fever can be beneficial, and many argue that antipyretic therapy can have a negative impact on the body by causing hypothermia and impairing the host's immune defenses.^{4,5,35} Fevers may increase the bactericidal effect of antibiotics and serum and can also decrease the pathogenicity of some pathogens.^{4,5,35} If an antipyretic is considered necessary, aspirin can be administered at a dosage of 10 mg/kg q12h PO.² If there is clinical suspicion of a fungal disease,

trial antifungal agents may be of use.

If the fever does not respond to antibiotics or antifungals, options include waiting to see if new diagnostic clues arise and considering an immunosuppressive trial of corticosteroids. A dramatic improvement should be expected within 24 to 48 hours of corticosteroid therapy in dogs with an immune-mediated FUI.^{2,5} It is important to inform owners about the risks of trial corticosteroids, such as allowing a fungal or bacterial infection to disseminate or further decreasing the chance to diagnose the problem, as with lymphoma. Ideally, during a corticosteroid trial, the dog should be hospitalized and monitored closely for adverse effects.⁵ Initial improvement does not equal successful treatment. One study⁷ revealed that treatment 24 hours before referral was associated with a statistically significant increase in the time to diagnosis. Therefore, it is suggested that, when possible, therapy be withheld or withdrawn in dogs referred for investigation of FUI.

Conclusion

The most common and important causes of FUI in dogs are infection, immune-mediated disease, and cancer. Using a logical diagnostic approach to FUI in dogs usually results in a definitive diagnosis. Sometimes, being patient and allowing new diagnostic clues to emerge by revamping historical information (via reassessing current information and possibly obtaining a more detailed history) and repeating physical examinations and simple laboratory tests is more desirable than proceeding with more invasive and expensive tests if the dog is stable. Communicating with the client is of utmost importance. A broad knowledge of the possible causative diseases and the ability to interpret specific diagnostic test results in the context of FUI in dogs are essential to diagnose the source of an FUI. **C**

Acknowledgments

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QuickNotes

The most common and important causes of FUI in dogs are infection, immune-mediated disease, and cancer.

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1. Which statement regarding the investigation of FUO in dogs is false?

- a. Two-view abdominal and three-view thoracic radiographs are recommended.
- b. Joint radiographs can aid in the diagnosis of an erosive immune-based polyarthritis.
- c. Thoracic ultrasonography should always be conducted, especially if abnormalities are not detected on thoracic radiographs.
- d. Dogs with infective endocarditis are usually medium to large breeds that do not tend to have myxomatous valve degeneration.

2. What is the correct definition of a true fever?

- a. increase in body temperature due to an elevation of the thermal set point in the anterior hypothalamus
- b. increase in body temperature due to an elevation of the thermal set point in the anterior pituitary gland
- c. a marked, rapid rise in body temperature without adjustment of the thermal set point in the anterior hypothalamus
- d. a marked, rapid rise in body temperature without adjustment of the thermal set point in the anterior pituitary gland

3. Which statement regarding fever in dogs is true?

- a. The cause of fever in most dogs is neoplasia.
- b. Most FUOs in dogs are caused by a common disease presenting in an obscure fashion.
- c. Dogs with true fevers commonly have prolonged body temperatures above 106°F.
- d. Prolonged body temperatures above 106°F are not dangerous.

- 4. FUO in dogs is commonly the result of _____ disease.**
- infectious
 - neoplastic
 - immune-mediated
 - all of the above
- 5. Which statement regarding sample culture is true?**
- A negative urine culture can rule out pyelonephritis.
 - A negative blood culture can rule out bacteremia.
 - A negative joint culture can rule out septic arthritis.
 - none of the above
- 6. When evaluating a dog with FUO,**
- it is usually not necessary to evaluate a blood smear in conjunction with the CBC.
 - a urine culture is only indicated when there is an active urine sediment.
 - repeated neurologic and fundic examinations are important.
 - a joint tap is recommended only for dogs presenting with lameness.
- 7. Which statement regarding blood cultures for dogs with FUO is false?**
- Blood cultures can be conducted for a dog currently on antibiotics.
 - It is rare for dogs with positive blood cultures to have isolation of the same organism from other sites.
 - Obtaining a larger blood sample volume is more important than the timing of the sample.
 - Bartonella* spp are emerging as an important cause of culture-negative infective endocarditis in dogs.
- 8. Which statement regarding arthrocentesis in the evaluation of a dog with FUO is true?**
- Only one joint should be tapped to decrease the chance of septic contamination.
 - Immune-mediated polyarthropathies tend to involve larger joints such as the stifles, elbows, and shoulders.
 - Degenerate neutrophils are not always seen with septic joints.
 - Immune-mediated polyarthritis is extremely rare in asymptomatic dogs with FUO.
- 9. Which statement is true with regard to dogs with FUO?**
- Antibiotics should never be started unless the definitive cause of FUO is determined.
 - A negative fungal antibody titer rules out infection with that organism.
 - Initial improvement after the start of corticosteroids does not equate to successful treatment because many diseases can respond favorably initially.
 - Bone marrow aspiration is only indicated if the CBC is abnormal.
- 10. Which statement is false with regard to dogs with FUO?**
- Using a logical approach usually results in a definitive diagnosis.
 - It is important to run as many diagnostic tests as quickly as possible when evaluating a stable dog with FUO.
 - Conduct fecal centrifugation and fecal cytology, if indicated.
 - If fever persists beyond 72 hours after a medication has been discontinued, a drug-induced fever can be ruled out.