The Diagnostic Approach to Fever of Unknown Origin in Cats*

True 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. With hyperthermic conditions other than true fever, the hypothalamic set point is not adjusted. Nonfebrile hyperthermia occurs when heat gain exceeds heat loss, such as with inadequate heat dissipation, exercise, and pathologic or pharmacologic causes.

Cats with true fever typically have body temperatures between 103°F and 106°F (39.5°C to 41.1°C). Cats are less likely than dogs to succumb to the dangerous effects of body temperatures greater than 106°F, which are usually seen with nonfebrile causes of hyperthermia. Temperatures less than 106°F are unlikely to be harmful in cats and may be somewhat beneficial because they constitute a protective response to inflammation.

The term fever of unknown origin (FUO) is used liberally in veterinary medicine. It should be used to identify a fever that does not resolve spontaneously, that does not respond to treatment with antibiotics, and for which the diagnosis remains uncertain after an initial diagnostic workup. Along with a thorough history and physical examination, initial diagnostics include a complete blood count (CBC), an FeLV antigen test, an FIV antibody test, a serum biochemistry profile, and urinalysis with antimicrobial culture. The cause of fever in most cats is infection that either is found during the initial workup or responds to antibiotic treatment; therefore, most cats do not have a true FUO.

**Differential Diagnosis**

Information regarding FUO in cats is extremely limited, and there are no retrospective studies. Fevers are common in cats, and most diseases associated with FUO in cats are infectious. Neoplasia is a less common cause of FUO in cats, and FUO due to immune-mediated disease is rare in cats. FUO causes are often separated into groups based on the underlying disease mechanism.

**Clinical Approach**

As in dogs, the diagnostic approach to FUO in cats must be targeted to each patient. It should be guided by history and physical examination findings, laboratory test results, and the potential causes common to the geographic location. A three-stage approach, such as the one presented in BOX 2, is commonly used. The goal of investigating an FUO is to promptly establish a definitive diagnosis while minimizing patient discomfort, client expense, and financial impact. A companion article about fever of unknown origin in dogs begins on page 14.

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*For more information on the clinical approach to cats with FUO, please refer to the clinical approach section in the article starting on page 14. Many of the same tests used in dogs can also be used in cats.
and invasive diagnostic tests. Communication with the owner is of utmost importance to ensure understanding of the time and financial commitment that may be required in order to obtain a definitive diagnosis.

If possible, all medications should be discontinued early in the evaluation to help rule out a drug-induced fever. If the fever persists beyond 72 hours after cessation of the medication, a drug reaction can be ruled out. Drugs that are known to induce fever in cats include tetracycline, sulfonamides, penicillins, and levamisole.

**History and Physical Examination**

Obtaining a thorough history is the first step to a successful diagnostic approach. The vaccination history should be ascertained because vaccines can cause immune-mediated fevers in cats during the immediate postvaccination period, and modified live virus vaccines can induce local lymphoid replication of the attenuated agent. Determining indoor/outdoor status, travel history, flea and tick control and potential exposure to diseases transmitted by parasites (e.g., hemotrophic mycoplasmosis, ehrlichiosis, bartonellosis, cytauxzoonosis), and contact with other cats is also important as many FUO causes are transmissible.

Knowledge of ingestion of prey species may be helpful because songbirds can carry salmonellosis, rabbits can carry tularemia, and rodents can carry plague or toxoplasmosis. Cats are frequently affected by stress hyperthermia, which must be ruled out before an extensive diagnostic evaluation is pursued. As in dogs, FUO diagnostic clues in cats are generally not readily apparent on physical examination, so repeated detailed examinations are essential. The whole body should be carefully palpated to detect subtle swelling or discomfort, which may help localize the fever source. The thorax should be gently compressed to evaluate for a cranial mediastinal mass. Repeated fundic examination should be performed because numerous infectious diseases (e.g., FIP, FIV, FeLV) cause ocular changes. Absence of ocular changes does not rule out infection with these diseases. Repeated neurologic and orthopedic examinations should be performed, although they can be difficult to interpret in an uncooperative cat.

**Feline Leukemia and Feline Immunodeficiency Virus**

FeLV antigen and FIV antibody blood tests should be conducted on every febrile cat. These tests are rapid and reliable, but it is important to understand how to interpret positive results.

**Fecal Examinations**

Fecal samples should be obtained from cats with FUO. If diarrhea is discovered, rectal cytology should also be conducted. Other diagnostic tests to consider include fecal flotation with centrifugation, direct fecal examina-

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**Potential Causes of Fever of Unknown Origin in Cats**

- **Bacterial infection (local or systemic):** Bacteremia, infective endocarditis, septic arthritis, osteomyelitis, diskospondylitis, septic meningitis, pyothorax, pyelonephritis, prostatitis, stumpy pyometra, peritonitis, abscess
- **Bacterial diseases:** Bartonellosis, borreliosis(?), mycoplasmosis (hemotrophic and non-hemotrophic), tuberculosis and other mycobacterial diseases, diseases caused by L-form bacteria (e.g., cellulitis or synovitis secondary to bite wounds or surgical incisions)
- **Viral:** FeLV, FIV, feline infectious peritonitis, feline calicivirus
- **Rickettsial:** Feline ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever
- **Fungal:** Histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis
- **Protozoal infections:** Toxoplasmosis, cytauxzoonosis, neosporosis(?), babesiosis(?), trypanosomiasis(?)
- **Immune-mediated diseases:** Polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, meningitis, steroid-responsive neutropenia and fever
- **Neoplastic:** Lymphoma, leukemia, multiple myeloma, necrotic solid tumors
- **Noninfectious inflammatory diseases:** Lymphadenitis, panniculitis, pansteatitis, pancreatitis, granulomatosis
- **Miscellaneous:** Portosystemic shunt, drug reaction, toxin, hyperthyroidism, idiopathic causes

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**Staged Diagnostic Approach to Fever of Unknown Origin in Cats**

**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.
- Conduct FeLV and FIV testing.
- Obtain samples for CBC, blood smear, and serum chemistry profile.
- Save serum for serology or other testing.
- Conduct a 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.
- Perform fine-needle aspiration with cytology of masses, lymph nodes, and fluids (cyst, pleural, peritoneal).
- Conduct blood culture.
- Perform 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 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.
- Perform bone marrow aspiration even if CBC results are normal.
- Perform biopsy as indicated.
- Perform bronchoscopy and bronchoalveolar lavage as indicated.
- Conduct cerebrospinal fluid analysis.
- Perform dental radiography.
- Consider computed tomography, magnetic resonance imaging, nuclear imaging, or positron emission tomography.
- Perform laparoscopy or thoracoscopy as indicated.
- Consider exploratory celiotomy.
- Administer trial antibiotic or antifungal (if indicated) therapy.

**CBC and Serum Biochemistry Profile**
Typically, the changes seen on the CBC and serum chemistry profile in cats with FUO are nonspecific but can help suggest the next diagnostic steps. A blood smear should always be evaluated along with the CBC to help identify morphologic changes, infectious organisms, or changes consistent with neoplasia. Serum should be saved at this point for future testing, if needed.

**Urinalysis with Culture**
A urine sample collected by cystocentesis (unless contraindicated) should be submitted for urinalysis with antimicrobial culture and sensitivity for every cat with FUO, regardless of the appearance of the urine. If the cat has a history of lower urinary tract disease, urine should be submitted for urinalysis and culture and sensitivity on multiple occasions because a negative urine culture does not rule out infection. A sample should be submitted for urine protein:creatinine ratio if proteinuria is present with inactive sediment.

**Cytology**
Fine-needle aspiration should be conducted on any suspicious masses, lymph nodes, fluid accumulations, or abnormal organs, and samples should be submitted for cytology (FIGURE 1). Impression cytology (nasal planum, skin lesion, feces, rectal mucosa) can also be conducted, if indicated.

**Serology**
Serum samples should be submitted for infectious disease testing (e.g., feline infectious peritonitis, bartonellosis, hemoplasmosis, rickettsiosis, anaplasmosis) if a disease is clinically suspected and if patient history suggests possible exposure. Toxoplasmosis serology (IgG and IgM) should be submitted for all cats with FUO. Natural clinical infections in cats with neosporosis have not been documented.
so testing for this disease may not be warranted.\textsuperscript{19} Serology for feline foamy virus (previously known as \textit{feline syncytium-forming virus}) can be conducted for cats with FUO and suspected joint disease.\textsuperscript{20}

**Blood Cultures**

Blood culture should be conducted for cats with FUO and suspected bacteremia. Typical signs of bacteremia in cats include anorexia, pyrexia, and shifting leg lameness.\textsuperscript{21,22} Vegetative endocarditis is uncommon in cats, but these animals typically have heart murmurs.\textsuperscript{21,22} Underlying predisposing causes for which patients should be evaluated include pyothorax, septic peritonitis, gastrointestinal tract disease, pneumonia, endocarditis, pyelonephritis, osteomyelitis, pyometra, and bite wounds.\textsuperscript{21} In a recent study,\textsuperscript{23} bacteremia was diagnosed in 66 cats over a 9-year period.

**Radiography**

Two-view abdominal and three-view thoracic radiographs should be obtained if the minimum database does not reveal the cause of the FUO. Cats with lower respiratory disease are frequently asymptomatic, so care must be taken to rule out primary or secondary respiratory problems.

**Ultrasonography**

Abdominal ultrasonography can be valuable in detecting lesions not seen on radiographs. It can also assist with fine-needle aspiration or biopsy if needed. Thoracic ultrasonography is not rewarding unless there are radiographic changes.

**Bone Marrow Evaluation**

Bone marrow aspiration should be performed early in the evaluation of cats with FUO if CBC abnormalities consistent with bone marrow disease are present (\textbf{FIGURE 2}). It should be considered later if no definitive diagnosis has been made, even if the CBC is normal, because neoplasia and infectious disease can cause FUO in cats.\textsuperscript{2}

**Arthrocentesis**

Arthrocentesis should be conducted on cats even if there is no obvious evidence of joint disease. Calicivirus, mycoplasmosis, L-form bacterial infection, and FeLV with feline foamy virus are all associated with polyarthritis in cats.\textsuperscript{24–27} Other infective arthritides include fungal, rickettsial, and protozoal diseases.\textsuperscript{28}

**Immunodiagnostic Screening Panels**

Immune panels (antinuclear antibody, rheumatoid factor [RF], Coombs) are thought to be unrewarding in cats with FUO, but in a recent study, 10 of 12 cats definitively diagnosed with rheumatoid arthritis were strongly seropositive for RF.\textsuperscript{2,8,29,30} Therefore, although RF is not specific for rheumatoid arthritis, it may be an important diagnostic test in cats. The study also stated that four cats diagnosed with periosteal proliferative polyarthritis were negative for RF.\textsuperscript{30} Antiplatelet antibody tests and serum protein electrophoresis can be conducted if thrombocytopenia or hyperglobulinemia, respectively, is present.

**Other Diagnostic Testing**

Other diagnostic tests, such as cerebrospinal fluid analysis and bronchoscopy with bronchoalveolar lavage or transtracheal wash, should...
Fevers may increase the bactericidal effect of antibiotics and serum and can also decrease the pathogenicity of some pathogens.\(^3,31\) Fever can result in considerable malaise, dehydration, and anorexia; therefore, clinicians must decide in each case whether NSAIDs could be beneficial.\(^3\) If an antipyretic is considered necessary, aspirin dosed at 10 mg/kg q48–72h PO can be used.\(^2,4\) Empirical antibiotic therapy should be based on the organ system involved or the infectious agent suspected.\(^5\) Trial antifungal therapy should be considered for cats with suspected fungal infections that cannot be proven. Trial corticosteroids can be considered in cats with FUO for which the cause cannot be identified, making sure to discuss potential complications with the owner before use.

**Conclusion**

Fevers are common in cats, and infectious disease is the most common cause of fever in cats. Using a logical diagnostic approach to a cat with an FUO will usually result 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 cat is stable. Communication 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 FUO in cats is essential to correctly diagnose the source of an FUO.

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**References**

1. An example of a true fever would be an elevated body temperature
   a. secondary to heatstroke.
   b. associated with a drug reaction.
   c. secondary to a prolonged seizure.
   d. secondary to malignant hyperthermia.

2. Stage 1 diagnostic testing for cats with FUO should include
   a. urinalysis.
   b. ultrasonography.
   c. arthrocentesis.
   d. biopsy.

3. _______ examination should be conducted repeatedly in cats with FUO.
   a. Physical
   b. Fundic
   c. Neurologic
   d. all of the above

4. Which is not known to be associated with polyarthropathy in cats?
   a. feline infectious peritonitis
   b. mycoplasma
   c. calicivirus
   d. L-form bacterial infection

5. The underlying predisposing causes of bacteremia in cats include
   a. pneumonia.
   b. pyelonephritis.
   c. gastrointestinal tract disease.
   d. all of the above

6. The most common cause of FUO in cats is
   a. neoplasia.
   b. infectious disease.
   c. immune-mediated disease.
   d. none of the above

7. _______ has been reported to cause FUO in cats.
   a. A portosystemic shunt
   b. Lymphadenitis
   c. Polyarthropathy
d. all of the above

8. Thoracic radiography should be conducted
   a. in all cats with FUO.
   b. if ultrasonography results indicate respiratory disease.
   c. if the minimum database does not reveal the cause of the FUO.
   d. only in cats with clinical signs of respiratory disease.

9. Which statement regarding fever in cats is true?
   a. Cats with true fevers typically have body temperatures between 103°F and 106°F.
   b. Cats are not affected by stress hyperthermia; therefore, a thorough diagnostic evaluation should immediately be conducted on every febrile cat.
   c. A subtle subcutaneous swelling on the limb of a febrile cat can be ignored because it is an unlikely cause of fever.
   d. About 50% of FUOs in cats remain undiagnosed despite thorough diagnostic evaluation.

10. Which statement regarding testing in cats with FUO is true?
    a. FeLV and FIV tests do not need to be conducted in cats previously tested for these diseases.
    b. A serum bile acids assay is never indicated in a cat with FUO.
    c. A blood smear should be evaluated along with the CBC for every cat with an FUO.
    d. Bone marrow aspiration is indicated only when the CBC is abnormal.